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THE HÆMADSORPTION VIRUSES IN LARYNGO-TRACHEO-BRONCHITIS.

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CROUP is a convenient term to describe a common syndrome which is almost confined to infants and young children. The illness is acute, with sudden onset, being characterized by stridor, a hoarse voice and frequently a harsh cough. This indicates, primarily, a laryngeal lesion with some degree of obstruction to breathing, but involvement of the trachea and bronchi is usual. The pathological change is one of acute inflammation so the lesion may be described as laryngo-tracheo-bronchitis. A clinical diagnosis is made, with a high degree of accuracy, by the experienced general practitioner, pædiatrician or infectious disease specialist. An account of the clinical features of croup, as seen in patients with severe attacks necessitating their admission to this hospital, has been given by Forbes (1961).

There is widespread belief amongst medical practitioners in Australia that mild forms of croup are usually allergic, but in our experience of patients requiring hospital treatment, anaphylactoid or allergic croup is a rare condition. Of bacterial infections only two—laryngeal diphtheria and supraglottic œdema—appear to initiate the croup syndrome. Laryngeal diphtheria is now an uncommon, though serious, occurrence in our immunized communities and supraglottic œdema, due to *Hæmophilus influenzæ* type B, is likewise an uncommon disease. Other bacterial pathogens, such as *Staphylococcus pyogenes, Streptococcus pyogenes* and *Strep. pneumoniæ*, appear to be secondary invaders and not primary agents in croup.

Over the past few years there has been evidence to suggest that the croup syndrome is nowadays, in most instances, viral in origin. In 1956 Chanock described a croup associated (CA) virus and later (Chanock *et alii*, 1958) two further agents named HA1 and HA2. These three hæmadsorption viruses, so-called because of their ability to adsorb red cells in infected tissue cultures, were grouped together and renamed *Myxovirus parainfluenzæ* types 1, 2 and 3 (Andrewes *et alii*, 1959). The CA virus became parainfluenza type 2, HA1 became type 3 and HA2 type 1. The Sendai virus, described earlier (Jensen *et alii*, 1955), was so closetly related to HA2 that it also became *Myxo. parainfluenzæ* type 1. During the 1957 Asian influenza pandemic in Melbourne there was epidemiological evidence that the Asian strain of *Myxo. influenzæ* type A was associated with croup (Forbes, 1958). Croup is not an uncommon manifestation in measles (Forbes, 1961). Other viral agents have been isolated from patients with croup—

certain adenoviruses, ECHO viruses, reoviruses and Coxsackie viruses (Chanock, 1958; Forbes, 1961)—but their ætiological significance is not yet firmly established.

It is the purpose of this paper to present the results obtained in a study of all patients with croup admitted to Fairfield Hospital over a 14-month period. Control groups of respiratory infections other than croup and of non-respiratory illnesses were studied in the same way. These data allow a critical assessment of the role of the parainfluenza viruses in croup. Preliminary findings have already been reported (Ferris, 1960).

Materials and Methods.

Tissue Culture Techniques.

Monolayer cultures of monkey kidney epithelium were grown in medium 199. The hæmadsorption technique as described by Shelokov *et alii* (1958) was used for the detection of the virus and, by specific neutralization with rabbit antisera, for the identification of strains.

Patients' Sera.

Serum specimens were obtained from 78 patients on admission to hospital and from 59 of these patients on discharge from hospital six or seven days later. A third serum sample was obtained from 29 patients 8 to 26 weeks after the onset of symptoms. Antibody to the three parainfluenza viruses was estimated by the neutralization method in tissue culture using fourfold serum dilutions and 100 $TCID_{50}$ (50% tissue culture infective doses).

Isolation of Virus from Throat Swabs.

Pharyngeal swabs were immersed in 2 to 3 ml. of medium 199 (*plus* antibiotics) contained in screw-cap bottles. On their arrival at the laboratory specimens were handled immediately, if possible, or alternatively held at 4° C. overnight. Bottles were agitated for at least five minutes on a mechanical shaker, then centrifuged at 2000 revolutions per minute for 10 minutes. The supernatant fluid was inoculated in 0·2 ml. amounts into each of two tubes of monkey tissue. During seven days' incubation at 36° C. on a roller drum, the cultures were examined twice for the presence of cytopathic change. If no change was observed, a blind passage was made into further monkey kidney tissues. Following another seven days' incubation, the supernate was removed and the tissues tested for hæmadsorption, whether or not cytopathic change was present. Cultures showing hæmadsorption were retained for identification.

Results.

All tissue culture tubes inoculated from throat swab specimens were tested for hæmadsorption over the period from April 1, 1959, to June 30, 1960. Throat swabs from 1965 patients examined in this way yielded 133 parainfluenza viruses comprising 85 type 1, 20 type 2 and 28 type 3 strains.

Many of the patients from whom swabs were examined had respiratory illnesses—299 were clinically recognizable as "croup" and the remainder were nondescript in character. Non-respiratory illnesses were miscellaneous, but the majority were thought to be enterovirus infections, and throat swabs were taken as part of the planned investigation. A comparison of parainfluenza virus isolation rates in three illness categories—croup, other respiratory illnesses and non-respiratory illnesses—is given in Table I.

It will be noted that of the 132 patients who yielded virus, 112 (84·8%) were suffering from croup and the isolation rate for croup was 37·4% compared with 2·8% and 0·3% in the two control groups.

The distribution of virus types is given in Table II.

The association with croup was slightly higher in the case of types 1 and 2 than in the case of type 3 strains, but the difference is not significant.

Virus isolations in croup listed according to age are shown in Table III.

It can be seen that the isolation rate steadily declines with advancing years. No good explanation can be offered. The youngest children were not admitted to hospital sooner than older children, nor were children who yielded virus admitted sooner than those whose swabs gave negative results. Of the whole group, 55% reached hospital within 24 hours, and 78% within 48 hours of the onset of the illness. It is possible that the older children may have possessed partial immunity to the parainfluenza virus type which brought them to hospital, owing to previous infection with one or more of the other closely related parainfluenza viruses.

TABLE I.

Comparison of Myxovirus Parainfluenzæ Isolations in Three Illness Categories.

Illness.	Number of Patients.	Number of Parainfluenza Viruses Isolated.
Croup	299	112 (37·4%)[1]
Other respiratory diseases ..	615	17 (2·8%)
Non-respiratory diseases ..	1051	3 (0·3%)

[1] One patient yielded two viruses (type 2 and type 3).

Over the 14-month period of this investigation the virus isolation rate was not constant, as shown in Table IV.

It is evident that all three viral types, although present throughout, had epidemic prevalence at different times. Total parainfluenza virus isolations showed fluctuations from quarter to quarter, but there was a notable increase in isolation rate in 1960, when types 1 and 2 were prevalent, perhaps indicating that these viruses were easier to isolate than type 3. There was no alteration in the age-group pattern in 1960 (that is, no increase in the proportion of younger children) which could explain this high isolation rate. An improvement in technique cannot be excluded, but we consider it more likely that other viruses, not demonstrable by the present techniques, may have been prevalent during the latter part of 1959.

TABLE II.

Distribution of Virus Types.

Type of Virus.	Total Number of Isolations.	Isolations in Croup.	Isolations in Other Respiratory Illness.	Isolations in Non-Respiratory Illness.
Myxovirus parainfluenzæ, type 1 ..	85	75	7	3
Myxovirus parainfluenzæ, type 2 ..	20	18	2	Nil
Myxovirus parainfluenzæ, type 3 ..	28	20	8	Nil

Total virus isolations from croup during May and June, 1959, when Asian influenza was epidemic, were amplified by the isolation of nine Asian influenza viruses, which we consider to be ætiologically significant, in addition to the parainfluenza viruses shown in Table IV. In addition there were six isolations of adenovirus (types 1, 2, 3 and 5) scattered in occurrence throughout the period of study.

In our experience survival of virus was of a low order in stored specimens. It appeared that specimens stored at 4° C. for more than one day (for example, in the week-end period) gave poorer results than specimens handled at once or after overnight storage at 4° C. Storage at −20° C. was not adequate to ensure survival of virus. Thirty specimens which all yielded *Myxo. parainfluenzæ* when handled immediately, or after being held overnight at 4° C., were retested after two to four weeks at 4° C. Only nine specimens now yielded virus.

In most cases swabs were taken one or two days after the onset of symptoms, but it was noted that an occasional

virus was grown as long as 10 days after the onset. Swabs were taken at 48-hour intervals from a series of patients who had been ill for less than 24 hours at the time of admission. Eighteen patients yielded virus from the first swab. Of the 18 patients, 17 yielded virus from the second swab, 10 from the third and only one from the fourth swab (taken on the seventh day after the onset).

TABLE III.

Virus Isolation Rates Listed According to Age.

Age in Years.	Number of Patients.	Number of Isolations.
0+	133	62 (47%)
2+	94	35 (37%)
4+	45	22 (21%)
6+	27	5 (19%)

TABLE IV.

Parainfluenza Virus Isolations from Croup in Succeeding Quarters.

Period.	Total Hospital Admissions.	Parainfluenza Viruses. Type 1.	Type 2.	Type 3.	Isolation Rates.
May and June, 1959	35	0	1	9	18%
Third quarter, 1959	52	2	0	4	
Fourth quarter, 1959	68	11	1	3	22%
First quarter, 1960	64	37	1	1	56%
Second quarter, 1960	80	25	15	2	

Paired serum samples, taken at intervals of approximately seven days, were available from 59 patients with croup. These were tested for neutralizing antibody to the three hæmadsorption viruses. Only four patients showed a fourfold or greater rise in antibody level, probably owing to the short interval between serum samples. A third serum was therefore obtained from 29 of the most recent patients at intervals of 8 to 26 weeks after onset and the neutralizing antibody titres of the first and third serum samples were compared (Table V). Among these 29 patients a definitive diagnosis of parainfluenza virus infection was possible from evidence of isolation of virus and/or serological evidence in 25 cases (83%).

It will be noted that none of the 14 patients from whom virus was isolated had detectable antibody to the infecting strain at the time the initial serum sample was taken. This is to be expected in an illness such as croup, which is an acute infection of a body surface with a probable short incubation period, which leads to an early admission to hospital. It follows that the presence of antibody to a specific agent on admission to hospital almost rules out that agent as the likely cause of a current attack of croup. Likewise it is to be expected that antibody would usually be absent at discharge from hospital six to seven days later, as was found here. That homologous antibody does develop at a later stage is shown by the findings in Table V.

Serum samples, taken on admission to hospital, were available from 78 patients with croup. Of these, 16 had antibody to type 1, 15 to type 2 and 69 to type 3, while only six had no antibody detectable to any type. The titres of these 78 sera are shown in Table VI.

These findings reflect experiences prior to the infection which brought patients to hospital and indicate the ubiquity of parainfluenza viruses in this community. The high proportion of children with type 3 antibody, and the higher titres shown, appear to be related to the type 3 epidemic which was subsiding at the time this investigation was commenced (see Table III).

Discussion.

Our findings support and extend those of other workers in establishing the three parainfluenza viruses as the important ætiological agents in the severer forms of croup. It would appear probable that most of the milder forms of croup, which are nursed at home, have the same ætiology, but direct evidence is lacking. Our supportive evidence comes partly from virus isolation and partly from serological studies.

It was found that parainfluenza viruses were isolated readily in croup (37·4% of cases), sometimes in respiratory illnesses which were clinically distinguishable from croup (2·8% of cases) and rarely (0·3% of cases) in the absence of respiratory symptoms. All three viral types show these

TABLE V.

Neutralizing Antibody to Parainfluenza Viruses in First and Third Sera from 29 Patients with Croup.

Patient.	Type of Parainfluenza Virus Isolated.	Type 1 Antibody.[1] First Serum.	Type 1 Antibody.[1] Third Serum.	Type 2 Antibody. First Serum.	Type 2 Antibody. Third Serum.	Type Diagnosis and Remarks.
I	1	0	4	0	0	1
II	1	0	8	0	0	1
III	1	0	8	0	0	1
IV	1	0	8	0	32	1 (rise in type 2 also present).
V	1	0	8	0	8	1 (rise in type 2 also present).
VI	1	0	8	8	32	1 (rise in type 2 also present).
VII	1	0	8	128	256	1
VIII	1	0	16	32	32	1
IX	1	0	32	0	0	1
X	1	0	32	16	32	1
XI	2	16	16	0	8	2
XII	2	0	0	0	16	2
XIII	2	0	0	0	32	2
XIV	2	32	16	0	32	2
XV	Nil	0	8	0	0	1
XVI	Nil	0	8	0	0	1
XVII	Nil	0	8	0	0	1
XVIII	Nil	64	128	0	8	2
XIX	Nil	4	0	0	16	2
XX	Nil	16	64	0	8	2 (possible rise in type 1 also present).
XXI	Nil	8	64	0	32	2 (rise in type 1 also present).
XXII	Nil	0	8	0	8	1 or 2
XXIII	Nil	8	16	8	64	2
XXIV	Nil	8	8	16	64	? 2 (doubtful rise in type 2 present).
XXV	Nil	0	0	0	0	3 (rise in type 3 from 16 to 128).
XXVI	Nil	0	0	0	0	Undetermined.
XXVII	Nil	0	0	0	0	Undetermined.
XXVIII	Nil	0	0	0	0	Undetermined.
XXIX	Nil	0	0	0	0	Undetermined.

[1] Antibody is expressed as reciprocals of initial serum dilutions (0=less than 4). Type 3 is omitted because all patients except Case VI had type 3 antibody in titres of 16 to 256+ in admission sera.

differing isolation rates, and in Melbourne (with a population of two millions) epidemics of the three agents have overlapped in varying degrees, as shown in our data. The data also suggest that another ætiological agent in croup, not detected by our techniques, may have been active during the currency of this investigation.

Our serological evidence is based on small numbers of observations, but several facts seem apparent. From the widespread distribution of antibodies in 78 acute-phase sera, it is evident that parainfluenza viruses are ubiquitous in this community and that therefore infections must frequently be mild or symptomless. Homologous

TABLE VI.

Titres of Neutralizing Antibody to Parainfluenzæ Viruses in Acute-Phase Sera from 78 Patients with Croup.

Antibody Titre.[1]	Number of Patients.		
	Type 1.	Type 2.	Type 3.
0	62	63	9
4	2	2	1
8	8	6	5
16	3	3	11
32	2	2	13
64	1	1	9
128	—	1	16
256 and 256+ ..	—	—	14

[1] Antibody titres are expressed as reciprocals of initial serum dilutions (0=less than 4).

antibody production was an accompaniment of virus isolation and there were significant rising antibody levels in many patients who failed to yield virus from throat swabs; this suggests that these, too, were parainfluenza virus infections. In all probably 25 of the 29 patients (83%) from whom paired sera were tested had suffered infection with *Myxo. parainfluenzæ*.

In a number of patients there were rising antibody levels to more than one virus type. On the evidence available we cannot decide whether this finding is a reflection of common antigenic components in the three parainfluenza viruses or is due to mixed or superadded infections. It is not possible to exclude cross-infection between patients in the croup ward, nor is it possible to exclude the possibility of fresh infections occurring in the community during the long interval which elapsed between the taking of the first and third serum samples.

Summary.

1. One of the three parainfluenza viruses was isolated from 37·4% of 299 children with croup, from 2·8% of 615 patients with other respiratory symptoms, and from 0·3% of 1051 patients without respiratory symptoms.

2. All three types of *Myxo. parainfluenzæ* appear to be ætiologically related to croup.

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A SYNCYTIAL VIRUS ASSOCIATED WITH EPIDEMIC DISEASE OF THE LOWER RESPIRATORY TRACT IN INFANTS AND YOUNG CHILDREN.

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AN agent which produced syncytial changes in tissue culture was isolated by Morris, Blount and Savage (1956) from an outbreak of respiratory disease in chimpanzees and named the "chimpanzee coryza agent" (CCA). Chanock, Roizman and Myers (1957) reported the isolation of two virus strains, indistinguishable from CCA virus, from infants with infections of the lower respiratory tract. Beem, Wright, Hamre, Egerer and Oehme (1960) found a clear-cut association between CCA virus and respiratory tract illness in infants, especially bronchiolitis and bronchopneumonia, and showed that the virus was isolated quite readily if fresh, unfrozen specimens were used. Later reports from Chanock and his group (1961) and from McClelland, Hilleman, Hamparian, Ketler, Reilly, Cornfeld and Stokes (1961) have confirmed these findings, and Kravetz, Knight, Chanock, Morris, Johnson, Rifkind and Utz (1961) were able to induce a common cold syndrome in adults by naso-pharyngeal inoculation with virus grown in tissue culture. The name "respiratory syncytial virus" was now adopted in place of "CCA virus". Cytoplasmic, eosinophilic inclusion bodies have been noted by Peacock and Clarke (1961), who quote Chanock as having observed them also.

In this laboratory, over two separate periods of time—July to November, 1960, and May to July, 1961—viruses which corresponded in tissue-culture behaviour and clinical association to respiratory syncytial viruses were isolated. This article gives a brief account of their properties and clinical association.

Material and Methods.

Throat-swab specimens were used for virus isolation. On arrival at the laboratory these were handled immediately, or held at 4° C. when taken at night-time or during week-ends.

Most isolations were made in trypsinized primary human kidney cultures, but primary human amnion and HEp-2 cells were also suitable. Although passage into trypsinized monkey-kidney monolayers has been successful, this did not appear to be the tissue of choice, and it is likely that the virus would have remained undetected had we relied entirely on monkey kidney as a source of epithelium.

The first virus isolates came from tissues incubated at 33° C., but it was soon determined that virus would grow equally as well at 36° to 37° C. The lower temperature of incubation had the advantage that cultures remained in better condition for longer.

Results.

Cytopathic changes usually appeared 6 to 10 days after inoculation of tissue cultures, and took up to four days to progress to maximal change. The characteristic feature was the presence of multinucleated syncytial masses, which were best seen in HEp-2 and human amnion cells. Syncytia were more difficult to distinguish in human kidney cultures, and the presence of "spongy" masses, which in

stained preparations consisted of cleared areas with central pyknotic nuclear remnants, were frequently the first evidence that syncytia had been present. In syncytial masses the nuclei tended to be centrally situated in human amnion and human kidney cultures, but in HEp-2 cultures nuclei were situated peripherally.

Eosinophilic cytoplasmic inclusion bodies, surrounded by clear haloes, were seen in preparations stained by hæmatoxylin and eosin. They were prominent in the early stages of syncytial development, but were less obvious in fully developed syncytia.

TABLE I.
Bronchiolitis, 1961.

Month.	Total Number Patients.	Respiratory Syncytial Virus Isolations.
February	1	—
March	1	—
April	2	—
May	1	1
June	16	14
July	7	3

Over the period July to November, 1960, we isolated syncytial agents from 19 patients. These strains appeared alike, but their identity was obscure. On analysis of clinical histories two striking features became apparent: first, all patients were infants or young children; secondly, the majority had left hospital with a final diagnosis of bronchiolitis.

TABLE II.
Respiratory Syncytial Virus Isolations: Ages of Patients.

Year.	Age in Years.						Total.
	0 and Over.	1 and Over.	2 and Over.	3 and Over.	4 and Over.	5 and Over.	
1960 ..	16	2	1	—	—	—	19
1961	32	7	3	1	1	1	45

The same techniques in tissue culture were followed, with brief lapses due to non-availability of human kidney, but no further viruses of this type were encountered until late May, 1961. Then, over a ten-week period, we isolated another 45 agents. This coincided with increased admissions to Fairfield Hospital of infants with bronchiolitis. Table I shows for the period February to July, 1961, the bronchiolitis patients investigated, and the total syncytial viruses isolated from these patients.

Syncytial viruses were also isolated at this time from young children suffering from croup, pneumonia and bronchitis. The 45 viruses isolated in 1961 spread over the four illness categories are as follows: laryngo-tracheobronchitis, 5/56 (8·9%); pneumonia, 8/35 (23%); bronchitis, 14/45 (31%); bronchiolitis, 18/24 (75%).

The very striking age incidence of patients who yielded syncytial virus from throat swabs is shown in Table II. Virus was not obtained from patients older than five years, and three-quarters of the patients who yielded virus were aged under 12 months.

Summary.

1. Our data indicate a characteristic syncytial virus associated with epidemic disease of the lower respiratory tract, especially bronchiolitis, in infants and young children.

2. A communication from R. M. Chanock states: "These viruses produced a morphological picture in tissue culture which is indistinguishable from that of respiratory syncytial virus."

3. A serological comparison between Australian and American viruses has not yet been completed.

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EPIDEMIC BRONCHIOLITIS CAUSED BY A RESPIRATORY SYNCYTIAL VIRUS: CLINICAL ASPECTS.

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IT is a function of Fairfield Hospital, Melbourne, to manage the severe and complicated cases which overflow from private practices and general hospitals during epidemics of respiratory disease. These admissions reflect, to a large extent, the epidemic state of Melbourne.

Two epidemics of bronchiolitis in infants, subsequently shown by Dr. A. A. Ferris and his colleagues to be due to a respiratory syncytial virus, were observed in this hospital in 1960 and 1961 (Lewis *et alii*, 1961).

For several years prior to July, 1960, the influenza and parainfluenza virus groups were the predominant causes of epidemic respiratory infections. In infants and young children, croup is commonly caused by influenza virus infection which is prone to predispose to pneumonia (usually pneumococcal). The parainfluenza viruses are also major causes of croup, but these viruses do not appear as potent as influenza in predisposing to pneumonia (Ferris, 1960; Forbes, 1960). These viruses had established a pattern of respiratory infection in Melbourne for several years, leading to the admission to hospital of fluctuating numbers of infants with croup and bacterial pneumonia.

In July, 1960, the pattern changed abruptly, with a sudden increase in the number of infants admitted with bronchiolitis and bronchitis and a concomitant increase in infants with pneumonia. These were not paralleled by an increase in croup or by a similar increase in pneumonia in older age groups. Prior to this, the diagnosis of bronchiolitis was infrequent.

Two hundred and forty-four children under the age of four years were admitted to hospital with the diagnosis of bronchiolitis, bronchitis or pneumonia during this epidemic. Fifty-eight *per centum* of the patients were

The epidemic in 1961 was replaced by an epidemic of influenza Type B, which, being a potent cause both of croup and of pneumonia, explains the variable admission rates in August and September (Figure I).

Clinical Features.

The clinical features of these epidemic groups were confirmed by detailed review of the records of the 70 patients from whom a respiratory syncytial virus was isolated.

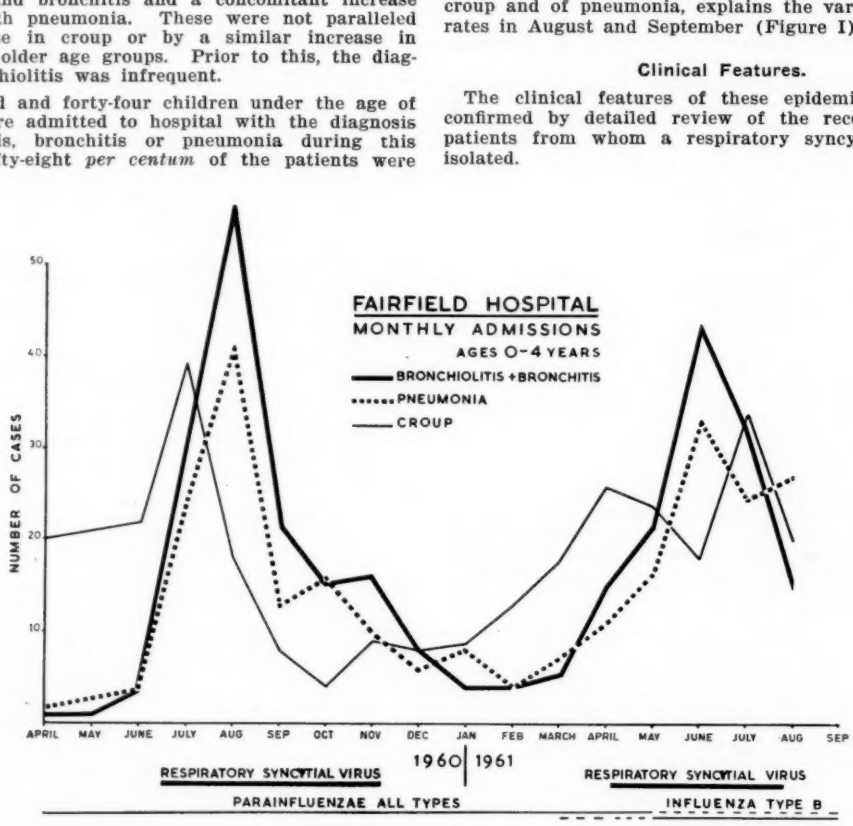

FIGURE I: Admission rates of patients, aged 0 to 4 years, to Fairfield Hospital during the two epidemics due to respiratory syncytial virus infection.

less than 12 months old, and patients under the age of four years dominated the group of respiratory infections in hospital at that time.

The major clinical feature of the group was the large proportion of infants in whom the observations of "wheezing" or "bronchospasm" associated with other evidence of pulmonary infection were made.

This epidemic pattern was repeated in April, 1961, when 237 patients under the age of four years were admitted, of whom 55% were aged less than one year.

Figure I shows the monthly admission rates of patients in the age group 0 to 4 years with bronchiolitis or bronchitis, bacterial pneumonia and croup. It can be seen that, during the two epidemic periods in question—namely, July to November, 1960, and April to August, 1961—the admission rates for bronchiolitis and pneumonia are parallel, but are independent of the admission rate for croup; this suggests a different causal agent.

The change in the pattern was striking in both epidemics, and it was apparent clinically that an agent other than influenza or parainfluenza virus was involved.

It was shown by Dr. Ferris and his colleagues that the croup in 1960 was due predominantly to parainfluenza virus infections, and that in 1961 to parainfluenza and influenza Type B viruses, whilst the infants with bronchiolitis and severe bronchitis yielded a respiratory syncytial agent not previously isolated.

The majority of infants had a history of two or three days' respiratory illness, often coryzal in onset. In some cases the onset occurred five or six days before the child's admission to hospital, cough developing after two or three days. In a few cases, the duration of symptoms before the child's admission to hospital was less than 24 hours.

In milder cases a diagnosis of bronchitis was appropriate; but in the more severe infections, which typified the groups admitted to hospital during these epidemics, the infants were pale, toxæmic and weak, with cyanosis of the lips and also of the extremities, which felt cold.

Dyspnœa with expiratory wheezing was characteristic. Difficulty in inspiration (differing from that seen in croup) was reflected in minor indrawing of intercostal soft tissue and failure of the chest to expand effortlessly.

There was at times evidence of coryza, with running nose and conjunctivitis. The pharynx was usually found to be mildly reddened in the manner seen in virus infections.

Tachycardia was present in all cases, whilst airway involvement was in evidence with inspiratory rhonchi and râles associated often with expiratory rhonchi. In some cases, no expiratory rhonchi were audible, even though wheezing was apparent on viewing the patient.

The persistence of bronchiolar obstruction, despite antispasmodic treatment, suggested that the wheezing was

due to inflammatory narrowing rather than to muscular spasm of bronchioles.

The leucocyte count in the blood was characteristically low, with an increase in the proportion of lymphocytes.

One outstanding feature of the condition was the disparity existing between the severity of the respiratory disease and the body temperature, which was often normal throughout the illness. When it occurred, elevation of the temperature was transient, lasting only a day or so except in those cases in which bacterial pneumonia had developed. There was disparity also between the severity of symptoms and the relative absence of X-ray findings. In some cases, however, pulmonary changes in the form of diffuse mottling were evident in the chest films.

The cough in some cases had a paroxysmal quality, which suggested the diagnosis of early pertussis.

Superficially, there may be diagnostic confusion between the wheezy cough associated with the dyspnœa of bronchiolitis, and the croupy cough, stridor and rib retraction of laryngo-tracheo-bronchitis.

The duration of the disease commonly varied between ten days and three weeks, being longer, of course, with superadded bacterial infection.

A minor number of patients with croup yielded a respiratory syncytial virus, but there was no evidence to suggest that this was a frequent outcome of the infection. This is shown by the disparity between the admission rates for croup and bronchiolitis in Figure I, which suggest that croup is merely an occasional effect.

Secondary Pneumonia.

In those cases in which bacterial infection occurred, there were additional signs of consolidation associated with grunting respiration. In these, the blood leucocyte count was usually raised, with a predominance of polymorphs, and localized pulmonary infection was apparent in the X-ray films.

The concomitant rate of admission to hospital of infants with pneumonia suggests that this virus is moderately potent in predisposing to pneumonia (usually pneumococcal) in these age groups. The correlation between these admission curves was confirmed by virus isolations (Lewis *et alii*, 1961).

The fact that this epidemic in infants was not associated with increased admission rates for older children and adults suggests either that the disease was relatively mild in the older age groups, or that they had immunity as a result of prior infection.

These observations conform with the recent descriptions in the United States and Great Britain (Chanock *et alii*, 1961; Editorial, *Brit. med. J.*, 1961; Editorial, *J. Amer. med. Ass.*, 1961; Editorial, *New Engl. J. Med.*, 1961; Johnson *et alii*, 1961; Kravetz *et alii*, 1961; McClelland *et alii*, 1961; Parrott *et alii*, 1961; Peacock and Clarke, 1961; Reilly *et alii*, 1961).

Treatment.

In view of the observed capacity of respiratory virus infections to predispose to bacterial pneumonia, and of the severity of the illness, all these patients were given antibiotics. Penicillin, which formed the basis of treatment in all cases in view of the likelihood of pneumococcal or streptococcal secondary infection, was supplemented by tetracycline in many for broader cover. Patients who were seriously ill, usually with cyanosis, received penicillin and chloramphenicol. Prednisolone was also used in these, but without dramatic effect. The more severely ill patients were managed in an oxygen tent.

Mortality.

Two deaths occurred in each epidemic. The ages of these patients were respectively six weeks, ten months, five months and three months. One death, in the patient aged six weeks, appeared to be purely due to the virus infection, whilst secondary bacterial pneumonia was present in the other three.

Histories of Contact.

Seventeen patients from whom virus was isolated in 1961 were reviewed six to twelve weeks after their discharge from hospital. Seven patients described minor cough or wheezing for periods up to one week after discharge from hospital. In eight families, siblings had similar related illnesses, and in three of these the parents also had respiratory diseases, which were described as "colds".

Summary.

Two epidemics of bronchiolitis in infants, subsequently shown to be due to a respiratory syncytial virus, were observed at Fairfield Hospital, Melbourne, in 1960 and 1961.

At the onset of each epidemic the pattern of respiratory disease established by influenza and parainfluenza infections changed abruptly, with a sudden increase in the number of infants admitted with bronchiolitis and bronchitis and a concomitant increase in the number of infants with pneumonia which appeared to be related clinically.

Two hundred and forty-four children were admitted to hospital during the first epidemic, 237 during the second. Two deaths occurred during each epidemic.

Outstanding clinical features were the large proportion of infants in whom the observation of "wheezing" was made, the disparity between the severity of respiratory disease and the body temperature, which was often normal throughout the illness, and also the disparity between the severity of respiratory symptoms and the relative absence of X-ray changes.

All patients received antibiotics, and in the more severe cases of bronchiolitis intensive oxygen therapy was required.

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THE NON-SURGICAL TREATMENT OF ENDOMETRIOSIS BY PROGESTOGENS.[1]

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Clinical Effects.

It is now over 50 years since the evidence for the importance of a corpus luteum was provided, and it was not until 1929 that the hormone responsible for the progestational growth of the endometrium after ovulation was extracted and its physiological efficacy demonstrated. During the last few years certain synthetic preparations have been discovered that have an effect the same as or even greater than that of the original progesterone itself. These newer substances have the additional advantage that they may be taken by mouth in most instances; they are called progestogens.

These synthetic progestogens have the following clinical effects: (i) a progestational effect on the œstrogen-primed endometrium; (ii) the suppression of ovulation when given in large doses; (iii) the suppression of spermatogenesis when given in large doses; (iv) hyperthermic effect on the basal body temperature; (v) an increase in the viscosity of cervical mucus; (vi) the postponement of menstruation when this is desired—for example, for such events as holidays, examinations or sporting events. Further biochemical effects are known at present and more remain to be discovered.

Kistner (1958) proposed that the progestational effect of these synthetic compounds on the endometrium should be utilized in the treatment of endometriosis or ectopic endometrium, after he had observed the changes brought about by normal pregnancy in causing regressive changes in such areas during a Cæsarean section. He conceived the idea of the establishment of an artificial or pseudopregnancy by their continuous administration for a number of months. The histological changes in the ectopic endometrium have been reported by several observers (Andrews, Andrews and Strauss, 1959; Kistner, 1959). Thomas (1958) utilized 17 alpha-hydroxy progesterone caproate ("Delalutin") instead of one of the progestogens for oral use.

In this paper are presented the results obtained from the use of these substances in the treatment of endometriosis in 83 patients, who have been studied either in private practice or in the Women's Hospital, Crown Street, Sydney.

It should be stated that these synthetic progestins have a different action when they are given after ovulation has occurred naturally than when they are administered throughout the whole month or for months on end. When they are taken after ovulation for five days they augment the normal secretory response of the endometrium. If they are taken throughout the month and prior to ovulation, they produce a distorted type of secretory endometrium (Grant *et alii*, 1959). The stroma becomes progressively decidual and florid, while the glands become empty of secretion, smaller and "exhausted".

Indications.

This method of non-surgical treatment does not supplant the usual surgical one consisting of conservative surgery for patients of child-bearing age and radical surgery later. Laparotomy or culdoscopy is still necessary to establish the diagnosis indisputably. There are two indications for the use of this supplementary progestogen therapy, namely (i) recurrent endometriosis in young women after a previous conservative operation, when they wish to achieve a pregnancy if possible, and (ii) as a preparation for operation on endometriosis to soften the endometriotic areas so that adhesions are more easily separated during the surgical manipulations.

[1] Read at the Annual Post-Graduate Course at the Women's Hospital, Crown Street, Sydney, in August, 1961.

Method.

The method used in this study is different from that employed by Kistner. He used these compounds continuously for about six months in order to stimulate the endometriotic areas to convert themselves into a decidua-like tissue which would undergo varying degrees of atrophy subsequently. The exact mechanism of this atrophy has not been explained. It was decided to find whether such a change would follow the intermittent administration of progestogens on a monthly basis instead of utilizing the continuous régime advocated by him. The advantage of such a method of therapy, if effective, was to be an economic one, as the cost of using increasing doses by the Boston regimen of continuous administration for six months placed this treatment out of the financial reach of most patients. The progestogen was therefore given in doses of 10 to 15 mg. a day from the fifth day after the onset of menstruation to the twenty-fifth day of the menstrual cycle, or for 20 days a month. This "day V to day XXV" sequence has been followed for six months. Some patients have yet to complete this programme.

Contrary to what is sometimes stated in the literature, this sequential therapy does not make the endometriosis worse, but produces an astonishing relief of the subjective symptoms, and pelvic examination shows that ovarian enlargements frequently diminish in size. Endometriosis in the recto-vaginal septum does not respond very favourably.

Material Studied.

Eighty-three patients in all were treated, amongst whom 67 had endometriosis proven at either operation or culdoscopy, and all of whom suffered disabling pelvic pain. It is well known that in about 25% of women who have this disease there are no textbook symptoms at all. No such cases have been included in the present series. Thirty of the patients had the problem of sterility, while the remaining ones were interested only in the discomfort caused by the disorder, and represented a cross section of any ordinary gynæcological practice.

The compound used in this group was mainly nor-ethisterone itself,[1] though a few patients received nor-ethisterone acetate. The latter preparation will soon be available on the Australian market. The dose of nor-ethisterone was 10 mg., and occasionally 15 mg., per day from day V of the menstrual cycle to day XXV.

The Results of Treatment.

The results of our method of treatment are set out in three tables. Table I shows the cure rate whilst the patients were taking the hormone by the prescribed cyclic programme and it will be seen that the majority of them experienced great relief. Numerous letters of appreciation were received of a type that it is not permissible to reproduce in a medical paper. Those patients who did not receive complete relief from their discomfort were in the majority of cases women who still had

TABLE I.
Relief of Painful Endometriosis during Progestogen Therapy.

Method of Making Diagnosis.	Total Number of Patients.	Number Relieved.	Number Not Relieved.
At operation or culdoscopy	67	57 (85%)	10 (15%)
On clinical grounds ..	16	14 (87%)	2 (12%)
Total	83	71 (86%)	12 (14%)

[1] Nor-ethisterone was generously donated by Schering A.G., Berlin. It is known chemically as 17 alpha-ethinyl 19 nor-testosterone. An experimental preparation containing a small quantity of added œstrogen was used in some cases. The trade name of the nor-ethisterone is "Primolut N".

dyspareunia from either recto-vaginal lesions or quite easily palpable ovarian cysts. Table II indicates the result of an evaluation made six months later, and it becomes obvious on a perusal of the table that there was a relapse rate of 20% amongst those who had been better whilst ingesting the tablets.

TABLE II.

Relief of Painful Endometriosis after Cessation of Progestogen Therapy.[1]

Method of Making Diagnosis.	Total Number of Patients.	Number Relieved.	Number Not Relieved.
At operation or culdoscopy	53	35 (66%)	18 (34%)
On clinical grounds ..	12	9 (75%)	3 (25%)
Total	65	44 (67%)	21 (32%)

[1] Patients evaluated after six months or longer.

The relative values of conservative surgery and progestogen therapy in bringing about pregnancy become clear on perusal of Table III, from which one can see that in our hands the operative approach yields over twice as many pregnancies. Only 30 of these women were interested in problems related to infertility, so that the pregnancy salvage rate in the group treated with progestogens is too small for us to accept 16% as the best result that can be obtained, and at present no final opinion can be given even on the basis of world figures, about the percentage incidence of subsequent pregnancy.

TABLE III.

Incidence of Pregnancy with Endometriosis after Treatment by Surgery and Progestogen Therapy Respectively.

Type of Treatment.	Total Number of Patients.	Number Achieving Pregnancy.
Conservative surgery ..	127	50 (39%)
Progestogen therapy ..	30	5 (16%)

There will probably never be any universal agreement about what time should elapse after progestogen therapy during which a pregnancy could reasonably be described as a propter-hoc event and not simply as a post-hoc accident.

During the six months following this hormonal treatment, 12 of the subjects in whom success had not been achieved were operated on, five having hysterectomies and seven undergoing some sort of conservative surgery because of a desire to achieve a pregnancy. Two of the latter group of patients promptly did become pregnant, which is consistent with previous experience with such operations, from which it seems that at least one-third of such patients do produce offspring. One of the patients who had a hysterectomy performed also suffered from fibroids, which increased rapidly in size during the time that the progestogens were administered. During the previous five years the tumours had remained relatively small, and were examined frequently by the same doctor. This stimulating effect of progestogens on fibroids has been noted by others.

Incidence of Side Effects.

We have used progestogens for the treatment of dysmenorrhœa, endometriosis, excessive fertility and functional bleeding by giving them throughout the menstrual cycle, and in all this work we have found that the patients who suffer from endometriosis complain of fewer side-effects than do women in the other categories. The use of these compounds in the post-ovular part of the cycle only appears to produce no unpleasant symptoms at all. Of all the minor complications the one that really causes consternation is amenorrhœa, and after that the most troublesome to the patient is "spotting" or break-through bleeding. Nausea usually occurs only in the first or second cycles of therapy, if at all, and disappears spontaneously.

Amenorrhœa in this series required no treatment if the patient was keeping a basal body temperature chart, as one could demonstrate a fall in temperature after the pills were stopped. In the absence of such a yardstick we gave an intramuscular injection of ethinyl œstradiol and hydroxy progesterone caproate ("Primosiston"), which caused vaginal bleeding several days later. If the patient can be persuaded that she is not pregnant, all that is necessary is to wait for five days to elapse after the end of the previous monthly course of tablets and start them once again for another 20 days. Break-through bleeding may be ignored unless it worries the patient. In this case an increase in the daily dose of the compound for a few days will usually stop the bleeding, which is always mild in any case, or a small dose of œstrogen may be added. Nausea is controlled by the use of antihistamines or antacid powders and is usually a non-recurrent symptom. These side-effects are not as formidable to deal with in practice as they may appear to be on paper.

TABLE IV.

Side-Effects of Progestogen Therapy in 242 Cycles in Patients with Endometriosis.

Side-Effect.	Number of Cycles.
Light or short periods	58 (23·9%)
Bloating and œdema	21 (8·6%)
"Spotting" or break-through bleeding..	14 (5·7%)
Amenorrhœa	5 (2·06%)
Nausea	30 (12·3%)
Other effects	4 (1·6%)
Total number of cycles with side-effects	132 (54·5%)

Discussion.

The results of our treatment of endometriosis by the intermittent and cyclic administration of progestogens are not as good for long-term relief as those from induced pseudopregnancy by the continuous use of increasing doses of the hormone over a number of months. The difference in permanent relief from symptoms after the cessation of therapy is about 20% less by the discontinuous method, as we were able to record about 67% relief after six months, whilst in the United States of America the comparable figure is 84%. Our mode of cyclic therapy has two advantages—namely, the smaller cost to the patient and the abolition of any worry about being pregnant. A number of patients treated by the continuous induction of pseudopregnancy (but whose histories are not here recorded in detail) kept calling at the surgery every few months "just to make sure" that they were not really pregnant.

When it is proposed to operate on a patient who is believed to have endometriosis, the preparatory use of these endocrine products for a few weeks will result in a considerable softening of endometriotic adhesions. These may be separated during the surgical manipulations without as much trouble as is usually encountered, and there are fewer of the annoying "pin-point bleeders" lying hidden in indurated fibrotic areas than are often found. These tiny, oozing points are resistant to being picked up by artery forceps in patients who have not been prepared

by progestogen therapy, and if not arrested they may cause post-operative morbidity.

If patients keep a basal body temperature chart during their progestogen therapy, it will exhibit a persistently elevated flat curve in the vicinity of 99° F. The pills are markedly thermogenic. There is a large field for research in regard to the more recondite biochemical effects of these progesterone-like synthetic compounds, but at present little information is available. Some fears have been expressed that these substances may "damage" the patient, but up to the present time no such ill-effects have been recorded. Within one or two months of the patient's ceasing to take them her ovulation returns to normal, if it was normal in the first instance.

It is our opinion that the best treatment for patients with infertility who are suspected of harbouring endometriosis is pelvic examination just before or during a period to see if the physical signs are exacerbated. When treatment is required, it should primarily be surgical for two reasons: firstly, the diagnosis is firmly established and secondly, conservative surgery yields a much greater salvage rate in regard to pregnancy, being over twice as effective. All surgeons should try the use of progestogen therapy in the month preceding operation.

Summary.

1. Progestogens are synthetic hormonal compounds with an effect on endometrium resembling that of progesterone, but differing from it in that the stroma is affected more than the glands, and when the progestogen is given for several weeks on end, ovulation is suppressed. If the progestogens are given only after natural ovulation for five days, there is no distortion of the secretory endometrium, but rather an augmentation of the normal secretory response in glands and stroma.

2. This action of progestogens on endometrium has been adapted for the treatment of ectopic endometrial deposits (endometriosis). It has been found that administration for months causes decidual transformation of endometrium, followed by some degree of atrophy.

3. This report deals with the treatment of endometriosis in 83 patients by progestogens given in an intermittent and recurring cyclic manner for six months.

4. All the patients so treated had symptoms of pain before or during the periods. Asymptomatic patients were excluded from the series.

5. Immediate relief of pain occurred in 86% of cases whilst the compound was orally ingested.

6. Six months or more later 67% of patients were still relatively free from symptoms.

7. The subsequent incidence of pregnancy in infertility patients was 16%.

8. The incidence of pregnancy following conservative surgery for endometriosis was much higher than this and amounted to 39% in our series.

9. This method of treating endometriosis is cheaper and less psychologically disturbing than the induction of pseudopregnancy by means of progestogen therapy, but apparently 20% less efficacious for permanent relief than pseudopregnancy.

10. Progestogens are useful for the treatment of other conditions, such as primary dysmenorrhœa, excessive fertility, functional uterine bleeding and the inadequate secretory endometrium.

11. Any form of continuous therapy with these synthetic progestational substitutes is complicated by some minor side-effects, such as short periods, nausea, "spotting", amenorrhœa or bloating. The treatment of these complications is described. They look worse on paper than they really are in practice.

12. This form of treatment is recommended for endometriosis that has recurred after previous conservative surgery, if there is any reason for wishing to avoid radical surgery temporarily.

13. Progestogen therapy and surgery are not competitive methods of treatment for endometriosis. The "pills" are indicated in a circumscribed and limited group of women who have this painful complaint.

14. Progestins given for a month prior to operation for endometriosis soften the endometriotic adhesions and make the separation of surgical planes much easier, with less oozing during the operation.

15. The percentages expressed in the tables are approximate, as the sample sizes are too small for accurate statistical analysis.

Acknowledgements.

We should like to thank the staff of the sterility clinic for their assistance, especially Dr. R. Mackey, Dr. R. Bowman, Dr. W. McBride and Dr. P. Deck. Sister N. Johnson supervised the records of the public patients and their follow-up and dealt with their numerous inquiries. The histological examinations were made by Dr. Murray Moyes, whom we wish to thank for his cooperation. He plans to publish these findings at a later date. We are also indebted to Schering A. G., of Berlin, for their supply of progestins, known in Australia as "Primolut N".

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THE TREATMENT OF HYPERCHOLESTEROLÆMIA BY MER-29.[1]

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THIS is the first report arising out of a long-term study in this Institute of hypercholesterolæmia and its relation to coronary artery disease. The broad aims of this study are (i) to study the genetic transmission of hypercholesterolæmia, (ii) to study the incidence and course of associated occlusive coronary artery disease, and (iii) to evaluate the ability of certain methods of reducing the serum cholesterol level to improve existing coronary insufficiency and to change the natural history of its development.

In one large and several smaller families residing in New South Wales we have found high incidences of hypercholesterolæmia and of coronary artery disease. In this report are described the initial results of therapy designed to lower the serum cholesterol level by the drug MER-29[2] in selected individuals from these families.

This compound, 1 p-(diethylaminoethoxy)-phenyl-1(p-tolyl)-2(p-chlorophenyl)-ethanol, interrupts cholesterol biosynthesis by inhibiting the conversion of desmosterol (24-dehydro-cholesterol) to cholesterol (Blohm *et alii*, 1959; Avigan *et alii*, 1960). Under its influence, significant amounts of desmosterol appear in the tissues and blood.

[1] This work has been supported by a grant from the Post-Graduate Medical Foundation of the University of Sydney.

[2] Wm. Merrell Pty. Ltd., North Sydney.

Since both desmosterol and cholesterol produce colour with the usual reagents used to measure cholesterol, special methods are necessary to differentiate and separately measure these two sterols in the serum of patients treated with MER–29.

Material.

Group I comprises eight members of the large family depicted in Figure I. The genetic and clinical findings in this family will be presented fully in a subsequent report.

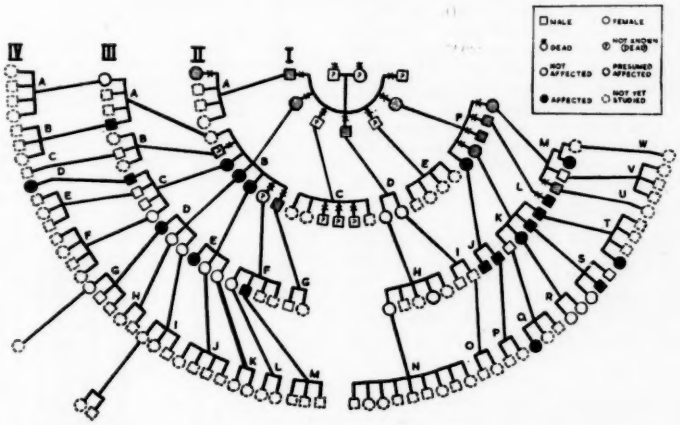

FIGURE I: Family with high incidence of hypercholesterolæmia (see text for code identification of individuals). Patients shown as "presumed affected" (hatched circles and squares) either had cutaneous manifestations of hypercholesterolæmia during life, or died of coronary artery disease. The majority of individuals in generation IV are in infancy or early childhood.

We now know of some 150 blood relatives. Nineteen of these have died, at least 10 of them from coronary artery disease. Of the 54 living relatives so far studied, 21 (39%) are hypercholesterolæmic (of these, seven have an arcus senilis, five have clinically apparent coronary artery disease, four have tendon xanthomas and one has xanthelasma).

Code numbers have been used to identify individuals in this family. A Roman numeral has been assigned to each generation and a letter to each sibship within a generation (both indicated in Figure I), and numbers in order of birth have been assigned to the members of each sibship. Thus patient III L1 is identified as the first-born in sibship L of the third generation.

The three patients in group II were not members of the above family, but were included in this trial for special reasons. All were grossly hypercholesterolæmic.

H.V., a woman, aged 31 years, had both ovaries removed at the age of 28 years in an operation for endometriosis, and two years later developed typical clinical and electrocardiographic signs of myocardial ischæmia; two out of four siblings, one parent and one aunt of this patient have since been found to have hypercholesterolæmia.

J.R., a boy, aged 17 years, has gross hypercholesterolæmia associated with tuberous xanthomatosis of the skin.

S.D., a man, aged 46 years, has primary hyperlipæmia with a very high serum cholesterol level.

Methods.

Lipid determinations have been made on the serum of venous blood drawn in the morning after an overnight fast. All sterol measurements have been made simultaneously by two methods, to make possible the calculation of the individual concentrations of cholesterol and desmosterol.

Franz *et alii* (1960) observed that these two sterols produce equal colour at 560 mμ with the Zak ferric chloride reagent (Zak *et alii*, 1954), but that desmosterol produces only about half as much colour as cholesterol at 620 mμ with the Lieberman-Burchard reagent. We have used the standard procedure of Abell (1952), and have modified the Zak method (1954) by applying the ferric chloride reagent to the petroleum ether extract of saponified serum obtained in the Abell procedure.

In our hands synthetic desmosterol[a] produces 56% of the colour given by an equal concentration of cholesterol in the Abell procedure, and 106% in the modified Zak procedure. When a serum sample containing both desmosterol and cholesterol is subjected to both procedures, individual concentrations of each sterol can therfore be calculated by solving the two simultaneous equations:

$$C + 0{\cdot}56D = R_A$$
$$C + 1{\cdot}06D = R_Z,$$

where C and D are the concentrations of cholesterol and desmosterol, and R_A and R_Z are the "apparent" cholesterol values obtained by the use of routine standards of cholesterol in the Abell and modified Zak methods respectively.

In practice we have divided the petroleum ether extract of saponified serum into four aliquots, two for the application of each colour reagent. Standards of cholesterol were run by each method on all occasions. Internal duplicate measurements by the Abell method showed an average difference from the mean of 1·3% (S.D. ± 1·5), and by the Zak method of 1·8% (S.D. ± 2·4).

Results by the two methods were not systematically different in the absence of desmosterol. For 130 serum samples, the Zak method gave a figure averaging only 2 mg. per 100 ml. (0·4%) higher than the Abell method. The absolute difference between the two results averaged 10 mg. per 100 ml. (S.D. ± 8).

In the cases in which MER–29 was not given, we have expressed the serum cholesterol level as the average result of the two methods. When MER–29 was given, and the results of the two methods differed by more than 26 mg. per 100 ml. (that is, by two standard deviations more than the average difference in the absence of desmosterol), separate concentrations of cholesterol and desmosterol have been calculated. On the few occasions when MER–29 was given and the two results were closer than this, we have recorded the Zak measurements only, as representing the total sterol concentration.

The ratio of free to esterified cholesterol was determined at intervals during treatment by the method of Zak (1954). When desmosterol was also present, we have assumed an equal ratio for both sterols (Steinberg *et alii*, 1960).

Phospholipid levels have been determined in milligrammes of inorganic phosphorus per 100 ml. of serum (Youngsburg and Youngsburg, 1930). Total serum fatty acid levels have

[a] Obtained through the courtesy of Dr. Joel Avigan, National Heart Institute, Bethesda, United States of America.

been measured in milliequivalents per litre by the method of Albrink (1959). Triglyceride fatty acid levels were then calculated by subtracting the amounts of fatty acid combined with cholesterol and phospholipids.

The average serum cholesterol level of 80 subjects (20 females and 60 males aged between 15 and 50 years) determined in this laboratory by the present methods was 216 mg. per 100 ml. (S.D. ± 43). To distinguish hypercholesterolæmic from normal subjects in this study, an arbitrary upper limit of normal of 280 mg. per 100 ml. has been used for the serum cholesterol level of patients under 40 years of age, and 300 mg. per 100 ml. has been used for that of patients over 40 years of age. Adequate definition of the normal limits of other serum lipid levels has not yet been obtained in this laboratory, but values so far conform to the following (Hallgren *et alii*, 1960): phospholipids, 6·7 to 8·7 mg. of phosphorus per 100 ml.; triglyceride fatty acids, less than 4·5 mEq/l. (equivalent to a serum triglyceride concentration of 130 mg. per 100 ml.).

Results.

Weight Reduction.

In five patients of group I weight reduction was feasible, and this was attempted formally over at least four months without other treatment. The total calorie intake was reduced, especially by restriction of fat; no attention was paid to the dietary cholesterol content. The results are shown in Table I. Significant and roughly proportional

TABLE I.

The Effects of Weight Reduction by Low-Calorie, Low-Fat Diets over Several Months in Five Patients from Group I.[1]

Patient.	Age, Sex.	Weeks of Treatment.	Pre-treatment Weight (lb.).	Weight Loss (lb.).	Pre-treatment Serum Cholesterol Level (mg. per 100 ml.).	Fall in Serum Cholesterol Level (mg. per 100 ml.).
II F1	62, F.	30	160	26	880	260
III C1	51, M.	17	164	3	425	25
III J2	36, M.	36	150	10	585	160
III K3	43, M.	18	187	30	700	300
III K4	34, M.	17	166	10	520	170
Mean ..	—	24	165	16	622	183

[1] Serum cholesterol levels fell by an average of 12 mg. per 100 ml. for each pound of body weight lost.

falls in the serum cholesterol level accompanied weight loss in every patient. The fall averaged 12 mg. per 100 ml. in the serum cholesterol level for each pound of body weight lost. In the two patients II F1 and III J2, continued observation without other treatment for two months after the body weight had become constant disclosed no tendency for the serum cholesterol level to rise again to its previous level (Figure II).

MER-29 Treatment.

A constant dose of 500 mg. per day of MER-29 was given, after weight reduction and stabilization, to five patients of group I, and without any dietary modification to the other three. Weekly or biweekly measurements of the serum lipid levels have been made, together with clinical studies as indicated, and periodical biochemical assessments of liver function.

Group I Patients.—In Figure II are shown the changes in body weight and in serum sterol concentrations during the two phases of treatment in patient II F1. This female, aged 62 years, presented (at week 0) with an acute posterior myocardial infarction. After her recovery dietary restriction was imposed and a satisfactory stable body weight was achieved. In week 31, MER-29 (500 mg. per day) was begun. The resulting falls in serum cholesterol and total sterol levels were not complete for about 10 weeks, but have been maintained now to week 66 without further change (Table II). Figure III shows the results of treatment in patient III K3, an asymptomatic man, aged 43 years, who had a serum cholesterol level of 600 to 700 mg. per 100 ml. when first examined. In his case, it was 11 to 12 weeks after MER-29 treatment had

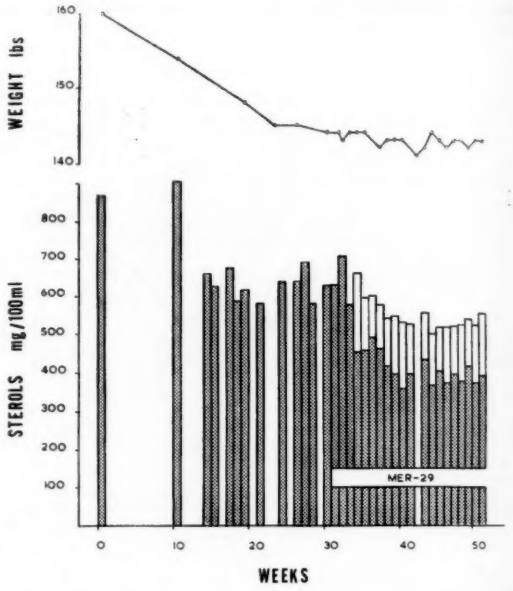

FIGURE II: Changes in body weight and serum sterol levels during treatment in patient II F1, a woman, aged 62 years (the height of each stippled bar represents the serum cholesterol level, and the white portion which appears during MER-29 treatment represents the serum desmosterol level).

begun before any fall in the serum cholesterol level was detected, and a steady level was reached after 13 weeks. The total sterol level during MER-29 treatment fell by an average of only 36 mg. per 100 ml., while the cholesterol level was reduced by 120 mg. per 100 ml. In this patient nicotinic acid (2 grammes per day) was added to MER-29, with the result shown; a further fall in the cholesterol level occurred (about 80 mg. per 100 ml.) without any change in the total sterol level. Observation for a further 10 weeks has confirmed this finding. The collected results in familial hypercholesterolæmia (group I) are given in Table II. A consistent fall in the serum cholesterol level was obtained, averaging 37%; the mean level reached, after an average of 23 weeks of treatment, was 269 mg. per 100 ml.—within our stated "normal" limit. The mean desmosterol concentration at this time was 120 mg. per 100 ml., which was 31% of the total sterol concentration. The drop in the total sterol level averaged 9%, significant falls occurring in six out of the eight patients. No definite or systematic change has occurred in the degree of esterification of serum sterols during treatment. No systematic change has been found in phospholipid levels. When the triglyceride level was grossly elevated before treatment (patients II F1, III D1 and III C1), substantial falls occurred; however, when the pretreatment level was close to the normal range little change was seen in four patients, and a marked rise was noted in one (II B4).

Group II Patients.—Patients H.V. and J.R. have shown very similar changes in the serum sterols during treatment with MER-29 (Table III); in addition J.R. has shown a very pronounced fall in the triglyceride level. In patient S.D. weight reduction and MER-29 treatment

TABLE III.

Results of MER-29 Treatment in Three Patients with Hypercholesterolæmia (Group II).

Patient (Code).	Age, Sex.	Weeks of Treatment.	Serum Sterol Levels (mg. per 100 ml.).			Serum Phospholipid Levels.		Serum Triglyceride Levels.		Body Weight (lb.).	
			Cholesterol (Before Treatment).	Cholesterol (After) Treatment).	Total Sterols (After Treatment).	Before Treatment.	After Treatment.	Before Treatment.	After Treatment.	Before Treatment.	After Treatment.
H.V.	31, F.	31	459	297	419	16·2	14·9	3·6	4·8	123	119
J.R.	17, M.	25	573	367	546	17·8	17·1	23·1	7·6	129	129
S.D.	46, M.	6	817	208	345	33·1	18·0	108	40·2	215	208

[1] Note that in patient S.D. weight loss and MER-29 treatment together have lowered the serum cholesterol level by over 600 mg. per 100 ml. The phospholipid levels are expressed in milligrammes of phosphorus per 100 ml. of serum, and the triglyceride levels as milliequivalents of fatty acids per litre.

were begun together; in Figure IV are shown the resulting pronounced changes in serum sterol levels. At the end of the ninth week, without his knowledge, MER-29 was replaced by a placebo preparation; both the cholesterol and the total sterol levels rose initially, but with continued weight reduction the cholesterol level fell again within two weeks. This result is presented to emphasize the importance of avoiding the effects of weight loss while evaluating drug therapy.

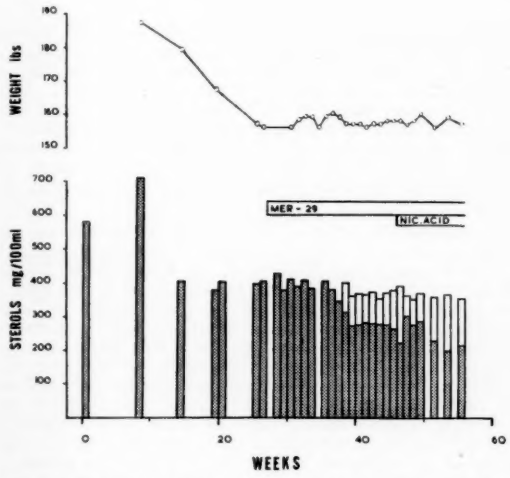

FIGURE III: Changes in body weight and serum sterol levels during treatment in patient III K3, a man, aged 43 years. (The stippled bar represents the serum cholesterol level and the white bar represents the serum desmosterol level.)

Clinical Results.—Four of the 11 patients had evidence of coronary artery disease at the time treatment was commenced. Patients II F1 and II B4 had severe myocardial infarctions during the previous 12 months; patient H.V. had typical clinical and electrocardiographic signs of myocardial ischæmia; a positive result to Master's test was obtained in patient III K2, although there was no clinical evidence of coronary artery disease, and her resting electrocardiogram was normal. In none of these four patients has there been evidence of progressive coronary artery obstruction during treatment. The two patients with previous infarction have both recovered fully, feel well and lead normal lives; their electrocardiograms show healed infarction. Patient H.V. has had considerable reduction in the frequency and ease of onset of anginal attacks; her electrocardiogram, which initially showed gross *S-T* segment depression and *T* wave inversion, has changed over 30 weeks of MER-29 treatment almost to normal. In patient III D1, Master's tests repeated during the fifteenth and twenty-first weeks of treatment both gave negative results and she remains asymptomatic. Four patients (II F1, III D1, II B4 and H.V.) have tendon xanthomas, and one (J.R.) has tuberous xanthomas; no appreciable change in the size of these lesions during treatment can be demonstrated.

Complications.—One patient complained initially of nausea after taking the morning tablet of MER-29; this disappeared when the tablet was taken after breakfast. No other gastro-intestinal disturbance has been noted. Two female patients (II B4 and III K2), after 28 and 23 weeks of treatment respectively, have noted abnormal hair loss from the scalp. In the case of patient II B4 this was mild, and had disappeared within three weeks after the dose of MER-29 had been reduced from 500 to 250 mg. per day. In the case of patient III K2 distinct recession of the frontal hair line occurred, with thinning of the scalp elsewhere. Treatment with MER-29 was discontinued for two months, by which time hair regrowth was established; the patient has recently recommenced treatment on a dosage of 250 mg. per day. No abnormality has been detected in monthly hæmoglobin measurements, white-cell counts or serum alkaline phosphatase level measurements.

Discussion.

The strong association between hypercholesterolæmia and coronary artery disease in the family reported here makes cholesterol depletion a logical treatment for affected individuals. We intend to apply such treatment over long periods, in an attempt to lower their otherwise inevitably high mortality and morbidity rates from arterial occlusion. In a careful study, Walker *et alii* (1953) showed that reduction of body weight regularly resulted in a fall in the serum cholesterol level, related in magnitude more to the initial cholesterol level than to the amount of weight lost. The present results are similar in that weight loss was always accompanied by a fall in the cholesterol level, which occurred during the period of negative calorie balance and persisted when body weight had become stable. However, the magnitude of the fall could be related either to the high initial cholesterol levels or to the amounts of weight lost (Figure I).

Despite satisfactory responses to weight loss in five cases, the average cholesterol level reached in them was still 439 mg. per 100 ml., and no weight loss was thought advisable in the remainder. The majority of affected members in this family are by no means overweight. The results of MER-29 treatment in these patients are consistent with the inhibition of cholesterol biosynthesis shown to occur in animals (Blohm *et alii*, 1959) and in man (Avigan *et alii*, 1960). The sustained reduction in the serum cholesterol level, averaging 161 mg. per 100 ml. in patients with familial hypercholesterolæmia after five months of treatment, is highly gratifying.

Other approaches to cholesterol depletion—by dietary cholesterol restriction, by the inhibition of its absorption by means of sitosterols or by an increase in its excretion brought about by thyroid hormone analogues—have usually provoked readjustments of cholesterol biosynthesis after a few months, with return of the serum cholesterol levels to previous values. This does not

TABLE II.

Changes in Serum Lipid Levels during Treatment with MER-29 in Eight Patients with Familial Hypercholesterolæmia (Group I).[1]

Patient (Code).	Age, Sex.	Weeks of Treatment.	Serum Sterol Levels (mg. per 100 ml.).			Serum Phospholipid Levels.		Serum Triglyceride Levels.		Body Weight (lb.).	
			Cholesterol (Before Treatment).	Cholesterol (After Treatment).	Total Sterols (After Treatment).	Before Treatment.	After Treatment.	Before Treatment.	After Treatment.	Before Treatment.	After Treatment.
II F1	62, F.	35	629	356	556	20·2	18·1	10·0	5·0	144	146
III D1	46, F.	23	349	201	336	13·8	14·6	12·6	6·1	115	113
III C1	51, M.	24	400	226	334	14·1	12·5	11·9	4·8	162	158
III J2	36, M.	28	434	324	426	14·6	14·4	3·5	3·5	140	140
II B4	68, F.	28	524	279	402	19·7	15·1	5·4	10·0	117	106
III K3	43, M.	15	402	278	366	13·2	14·3	4·8	8·0	157	157
III K2	52, F.	21	306	213	307	12·8	11·5	3·4	3·0	124	122
III K4	34, M.	12	399	277	389	—	—	—	—	156	160
Mean values	—	23	430	269	389	15·5	14·4	7·4	5·8	139	138
Mean changes	—	—	—	−37%	−9%	—	−7%	—	−22%	—	−1%

[1] The pre- and post-treatment values given are each the average of several weekly measurements. Weight reduction, if indicated, was carried out before MER-29 treatment was begun. Phospholipid levels are expressed in milligrammes of phosphorus per 100 ml. of serum, and triglyceride levels as milliequivalents of fatty acids per litre.

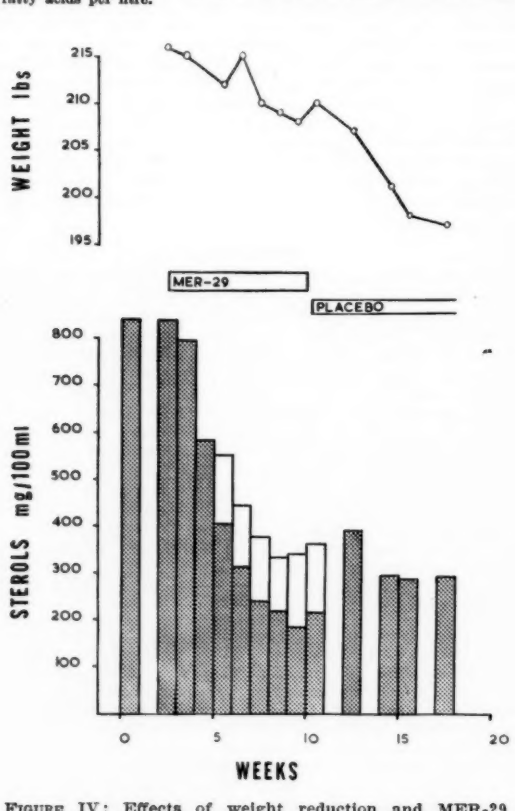

FIGURE IV: Effects of weight reduction and MER-29 treatment instituted together on serum sterol concentrations in patient S.D. (The stippled bar represents the serum cholesterol level, and the white bar represents the serum desmosterol level.)

appear to occur when MER-29 is used. We have encountered no instance of "escape" from the drug's influence during treatment periods up to 35 weeks.

It is obviously too early to assess changes occurring in the arterial circulation of treated patients, but at least no progression of disease has been detected. Patients II F1 and II B4 not only have lost all symptoms of myocardial ischæmia, but convincingly describe an unprecedented sense of well-being. Patient H.V. claims that she is far better than at any time since the onset of anginal pain two years ago, and her electrocardiographic changes are in accord with this. Prolonged survival and lowered incidence of coronary disease will ultimately be the criteria of successful treatment in this family.

The side-effects encountered are not troublesome, with the exception of hair loss in patient III K2; it remains to be seen whether this will recur on a dosage of 250 mg. per day of MER-29. In this regard, it is to be expected that large doses (1000 mg. per day) of MER-29 will cause disturbances in areas of the body in which cholesterol metabolism normally plays an important part. The pronounced epidermal changes described by Achor *et alii* (1961), and the changes in adrenal steroid hormone output found by Melby *et alii* (1961) are therefore not surprising; indeed they constitute good evidence that the drug is highly active. We have encountered no toxic effects of the drug on the liver or the bone marrow.

Judged from the viewpoint of cholesterol depletion, the results of MER-29 have therefore been highly satisfactory. Whether desmosterol accumulation will prove to antagonize, nullify or even reinforce the presumed retarding influence of cholesterol depletion on atherogenesis is clearly a very important consideration which cannot be decided at present. The reduction in total sterol levels (by 9% in this study) has recently been ascribed by Blohm *et alii* (1960) to a diversion of desmosterol or its precursors into bile acids under the influence of MER-29.

Changes in other serum lipid levels during treatment are difficult to interpret; no activity of MER-29 other than a specific inhibition of desmosterol reduction has yet been detected. However, it is of interest that considerable falls in the serum triglyceride level were noted in all three patients who had high levels at the beginning of treatment. The surprising apparent enhancement of MER-29 action by nicotinic acid in patient III K3 (Figure III) is being investigated further, in the hope that it may contribute towards the understanding of the cholesterol lowering action of nicotinic acid alone. The effect of the combination of MER-29 and nicotinic acid on the serum cholesterol level has been noted before (Estes, 1960), but no observation was made that nicotinic acid reinforced the specific activity of MER-29. In fact, it has always been assumed on a-priori grounds, that

nicotinic acid exerted its cholesterol lowering action in the early steps of synthesis involving coenzyme A, but this may prove incorrect. Of course, it is possible that our indirect serum measurements are no longer valid when nicotinic acid is present; probably gas chromatographic analysis of serum sterols will prove necessary for this study.

The results of MER–29 action in this family of hypercholesterolæmics differ in no essential way from the results obtained in normal subjects, and in patients with non-familial hypercholesterolæmia, either in this laboratory or in others (Steinberg *et alii*, 1960). This suggests that the final pathway of cholesterol biosynthesis in these patients does not differ from the normal. There is a longer latent period before a fall in the cholesterol level is detected in our patients than in other treated patients. This is partly the result of our reluctance to calculate small desmosterol concentrations by our methods of measurement, but is also probably due to the very high body pool of cholesterol present in these patients at the beginning of treatment.

Finally, it should be reemphasized that during MER–29 treatment, measurements of serum cholesterol levels by the standard methods used in most biochemistry departments will give readings higher than the true cholesterol levels by an amount depending on the method chosen and on the proportion of desmosterol present. This fact must be remembered in the assessment of the effect of MER–29 in clinical practice on the serum cholesterol level, but may not be important in the widespread use of this drug to treat hypercholesterolæmic patients with arterial disease.

Summary.

A preliminary report is given of a large family in New South Wales afflicted with familial hypercholesterolæmia.

Because of a very high associated incidence of early coronary artery disease in affected members, treatment designed to reduce the serum and body cholesterol content has been commenced.

Whenever feasible, weight reduction was advised, and produced substantial lowering of cholesterol levels during the periods of negative calorie balance.

Additional treatment with MER–29 was given to eight members of the family for average periods of five months. The mean pretreatment cholesterol value of 430 mg. per 100 ml. fell by an average of 161 mg. per 100 ml. to 269 mg. per 100 ml. after 10 to 12 weeks of treatment, and was maintained at this low level throughout treatment. Desmosterol, a precursor of cholesterol, accumulated to an average level of 120 mg. per 100 ml., finally constituting 31% of the total amount of sterol present in the serum.

The convenience of MER–29 treatment, and its low incidence of side-effects, make possible effective, prolonged cholesterol level lowering in hypercholesterolæmic subjects. This treatment would seem indicated in all such patients suffering or likely to suffer from occlusive arterial disease.

Acknowledgements.

Our gratitude is due to the staff of the biochemistry department of the Hallstrom Institute of Cardiology, and to numerous medical colleagues for their cooperation in this study. MER–29 and placebo tablets were generously supplied by Wm. Merrell Pty. Ltd., North Sydney.

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A REALISTIC APPROACH TO OPERATIONS FOR STRESS INCONTINENCE.

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SELDOM has a subject received so much attention in the medical literature, and yet become so confused by the many various and often conflicting views expressed upon it, as stress incontinence in women. This is the inability to maintain urinary continence under conditions of sudden increase in intraabdominal pressure as in sneezing, coughing and lifting, and it is a very common and distressing condition which has proved difficult to cure in a large proportion of cases.

Realizing that the surgical procedures usually employed in the treatment of prolapse were not achieving the desired results, some years ago the writer set out to examine the whole problem afresh. The recurrence rate was far too high—more than 30%—and the dyspareunia rate was in the region of 50%. By dyspareunia rate is meant the proportion of patients who, after operation for prolapse, have not been able to have intercourse without difficulty or pain. In an article entitled "A New Approach to Operations for Prolapse" (Loxton, 1955) an attempt was made to explain why operations in the past had failed, and how, by adhering strictly to certain primary anatomical and surgical principles, one could develop new operative techniques which would produce better results—results more in keeping with the rapid improvements being made in other branches of surgery. It was believed that it should be possible to cure prolapse and at the same time to preserve coital function. This function depends largely on the preservation of all vaginal skin. There is no mucous membrane in the vagina—its covering consists of stratified squamous epithelium. To refer to it as vaginal mucosa is, of course, quite wrong. Prolapse of the lower third of the anterior vaginal wall with stress incontinence, which forms a large part of the problem of prolapse, and is a rather more intricate subject, was not specifically dealt with at the time, but was reserved for a separate paper.

History.

In his famous work on the art of obstetrics, William Smellie (1876) refers to stress incontinence. It was probably as common a complication of childbirth then as it is today. Attempts to cure it during the latter part of the nineteenth century resulted in a large number of operations, many of which, by reason of their crudeness and barbarity, would find a more fitting place in a chamber of horrors than in a textbook of modern surgery; they included ligation of the urethra and the deliberate creation of a vesico-rectal fistula, suprapubic cystostomy, ureterocolic implantation, dissection and mobilization of the entire urethra with its reimplantation directly beneath the clitoris after rotation in its long axis through 180° or even 360° and wedge-shaped or diamond-shaped excisions of the urethral transitional epithelium and vaginal skin *en bloc*, followed by attempted repair of the defect. The object of the last-mentioned operation was to narrow the obviously dilated urethra.

The matter was later placed on a more scientific basis (Kelly, 1913; Kelly and Dumm, 1914). Realizing that the condition was due to a defect in the vesical sphincteric mechanism associated with dilatation of the urethra and usually, though not always, with prolapse, for the previous 13 years Kelly had set out to plicate the urethra and that portion of the sphincter which surrounds its upper end. He used two or three mattress sutures of silk superimposed on one another and so placed as to pick up the endopelvic connective tissue 1 to 1·5 cm. lateral to the urethra on either side, uniting these two points and the tissue lateral to them beneath the proximal end of the urethra and bladder neck. He then repaired the prolapse by uniting the usual flaps, after excising a diamond-shaped or elliptical area of vaginal skin with the subjacent endopelvic connective tissue attached. It is now generally agreed that in about 70% of cases, stress incontinence can be cured by this method or some modification of it.

A much more extensive and complicated dissection of the urethra from the vaginal aspect was performed by Kennedy (1937*a*, 1937*b*). In addition Kennedy divided the entire mass of endopelvic connective tissue lateral to the urethra and bladder neck, separating it from its peripheral attachments to the bones of the pelvis. So extensive was this dissection that one distinguished surgeon reported that, in endeavouring to follow it, he had inadvertently divided one of the ureters. The object of this technique was to repair the sphincter after having divided all its peripheral attachments. The rationale was that whereas in other parts of the body a voluntary sphincter possesses a peripheral attachment, an involuntary sphincter, as in the case of the alimentary tract, does not. Scar tissue liable to form as a result of damage at childbirth caused fixation of the sphincter to the pelvic bones and by its contraction prevented satisfactory closure of the urethra.

Appreciating the importance of the vesical sphincteric mechanism, dilatation of the urethra and prolapse, but in the belief that the latter could not always be repaired from below, Aldridge reintroduced and popularized an operation performed from above adding a modification of his own to it (Aldridge, 1942). In its essentials the operation practised for many years by continental surgeons (Gobell, 1910; Stoeckel, 1917; Hans, 1925, 1929; Baumm, 1931; Cramer, 1929) aimed at elevation of the bladder neck by a so-called fascial sling, or more accurately a strip of tendinous tissue or aponeurosis. Hans employed strips of aponeurosis cut from the rectus sheath, which were attached laterally to their respective muscle fibres in the external and internal oblique muscles, and, by means of a transverse lower abdominal incision, were made to pass through the cave of Retzius or retropubic space and sutured so as to lie beneath and behind the proximal part of the urethra and bladder neck. In addition Aldridge employed a step of his own designed to narrow the urethra and repair the sphincter from below.

At first it was believed that the muscle fibres, with their blood supply and nerves attached, would continue to function in a reflex manner, elevating the bladder neck still further with each sudden increase in intraabdominal pressure. That this is not so has been stated by Jefferson (1949), who considers that the slings become inactive a few days after operation. Marshall (1949) and Arthur (1949) have shown that the sling soon becomes replaced by a mass of fibrous tissue. McLaren (1957) in two repeat operations found no evidence of the previous slings. An operation similar in many respects was described by Millin and Read (1948). Barnes (1950) used the detached proximal ends of the round ligaments to support the bladder neck. The pubo-coccygeus muscles or strips cut from them have been employed by Squire (1911), Reddington (1948), Ingelman-Sundberg (1947, 1952), Treahy and Pacey (1948) and Bailey (1954). Later Ingelman-Sundberg (1957) utilized strips of vaginal skin cut from either side of the vagina, but remaining attached centrally to the proximal part of the urethra. Every structure in the vicinity, as well as others which could be used, has been used to support the bladder neck.

Elevation of the urethra and bladder and fixation of these structures to the back of the pubes was advocated by Marshall, Marchette and Krantz (1949). Through a midline suprapubic incision, the paraurethral and paravesical tissues were sutured to the periosteum covering the supero-posterior surface of the pubic bones, a series of two or three chromicized catgut sutures being placed on either side of the urethra. They claimed 82% of cures. Believing in the proposition suggested by Kennedy (1937*a*, 1937*b*) that fixation of the sphincter to the back of the pubes by scar tissue interfered with its function, Mulvaney (1951, 1952) devised an operation whereby the bladder and urethra were freed and separated from the back of the pubes, and the attachments of the sphincter to the pubic bones and pubo-ischial rami were deliberately divided. This was effected by an approach sometimes from above and sometimes from below. The principles of this operation of vesicourethrolysis are directly opposed to those of vesicourethropexy of Marshall, Marchette and Krantz (1949). However, good results have been claimed for both these procedures.

After a large series of opaque medium X-ray investigations of bladder function in normal subjects and patients with stress incontinence, Jeffcoate and Roberts (1952*a*, 1952*b*) noted, in the latter, descent of the bladder neck, funnelling of the proximal half of the urethra and loss of the posterior urethro-vesical angle. Of these three, loss of the posterior urethro-vesical angle appeared to be the commonest. They have laid great stress on this and consider it to be the most significant finding. In their view any operation which does not restore this angle to its normal 100° is likely to fail. Jeffcoate and Roberts (1952) advocated the Aldridge sling operation as the most effective means of restoring the urethro-vesical angle. So far they had not found any technique which would correct funnelling of the proximal part of the urethra. In 1956 Jeffcoate published the results of 44 operations, with follow-up periods from six months to 10 years, and claimed a cure rate of 86% (Jeffcoate, 1956).

However, sling operations are major and lengthy procedures, involving in many cases a combined abdomino-perineal approach. There is an appreciable mortality rate (Chalmers, 1952; Jeffcoate, 1956). Morbidity from vesical and urethral fistulæ, sloughing of the urethra, partial or complete obstruction of the urethra, infection of the retropubic cellular tissue, loss of micturition reflex, chronic over-distension of the bladder and chronic urinary infection have all received mention. Perrin (1946), McIntosh Marshall (1949), Moir (1950), Badnock (1950), Heyn (1950) and McLaren (1950) have all drawn attention to the dangers and difficulties of the operation. Bailey (1956) and Mulvaney (1957), in reviewing their results, have found it necessary to divide stress incontinence into a number of types and subtypes with a particular operation designed to cure each type. Ingelman-Sundberg (1957) now advocates a sling operation in which strips of vaginal skin are utilized.

A review of the literature on this subject is a formidable task. From my endeavours in this regard and from my

own experience it has become quite apparent that the surgical treatment of stress incontinence as usually carried out is still unsatisfactory.

Anatomy.

The anatomy of the vesical sphincteric mechanism is not precisely known. The voluntary and involuntary muscle fibres are so small, so diffuse and so scattered throughout a matrix of endopelvic connective tissue that a very difficult and time-consuming dissection will be necessary before it is known. This will involve the cutting of many thousands of serial sections, differential staining, examination and correlation of the muscle fibres into a composite picture of the sphincter and its peripheral attachments. There are some who doubt the existence of any sphincter at all (Denny-Brown and Robertson, 1933; Barrington, 1928). These workers believe that urinary continence depends on zero pressure within the resting bladder and apposition of the tissues around the meatus. In their view there is no voluntary or involuntary muscle constantly on guard.

From my own dissections (Figure I) I am quite certain, not only that a vesical sphincteric mechanism exists, but that the general arrangement of its larger muscle bundles

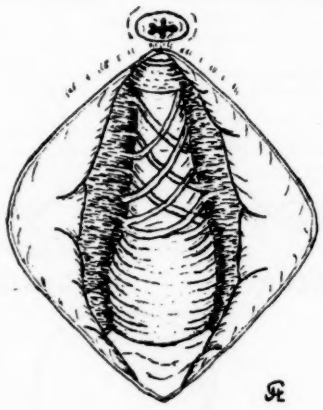

FIGURE I.

can be seen with the naked eye and studied more closely with a lens. If the former view was correct, then the bladder would be the only hollow viscus in the body acting as a reservoir which is not guarded by a sphincter. That the sphincteric mechanism consists of at least two parts—namely an internal, involuntary and an external, voluntary sphincter—is supported by the work of Wesson (1920), Martius (1954) and Jeffcoate and Roberts (1952*b*) and by analogy with the male.

There are grounds for believing that in the female there is a relatively stronger internal, involuntary sphincter surrounding the proximal two-thirds of the urethra and a relatively weaker external, voluntary sphincter surrounding its lower third and lying mainly within the urogenital diaphragm. The condensation of muscle fibres is greatest around the upper third of the urethra, where their distribution is mainly circular. Around its middle third the condensation is much less, and its fibres are oblique and cross one another Around its lower third the muscle fibres, which are voluntary, are again condensed and arranged in a circular manner. Laterally the muscle fibres appear to merge with the endopelvic connective tissue, but their distribution is obscure.

Physiology.

Considerably more is known about the physiology of the vesical sphincteric mechanism than about its anatomy. Much valuable information on the changes which take place in intravesical and intraurethral pressure under various circumstances has been obtained by cystometric and sphincterometric studies employing rubber or "Latex" balloons connected to a manometer and placed within the bladder by Barnes (1940) and Roberts (1953), and within the bladder and urethra by Yussef and Mahfouz (1956). Cysto-urethrography, or the study of serial X-ray (and in some cases rapid serial X-ray) pictures of the bladder and urethra outlined by a radio-opaque solution of sodium iodide and "Lipidiol" placed within the bladder and in bladder and urethra respectively, has demonstrated the various changes in position and outline of these structures under conditions of rest, straining, micturition and forced interruption of micturition in the normal subject and patients with stress incontinence, by Norris and Kimborough (1928), Schubert (1929), Mikulicz-Radecki (1931), Millin and Read (1948), Mullner (1949), Jeffcoate and Roberts (1952) and Roberts (1953).

In its function as a reservoir the bladder normally appears to be able to accommodate between 200 and 300 ml. of urine entering it through the ureters, without the subject having the desire to micturate; the intravesical pressure remains below 10 cm. of water. As more urine enters the bladder the pressure rises slightly and the desire to micturate is experienced (Roberts, 1953; Youssef, 1956). For various reasons this desire may be suppressed by inhibition of the detrusor muscle and increase in tone of the sphincter, in which case the intravesical pressure returns to less than 10 cm. of water. This process may be repeated several times. Eventually, when the amount of urine in the bladder has reached 800 ml. or more the pressure rises to 30 cm. of water. This initiates a series of detrusor contractions painful to resist. When the pressure reaches 100 cm. or more involuntary micturition takes place (Mulvaney, 1957). During micturition the intravesical pressure rises to between 30 and 50 cm. of water and is maintained at this level practically throughout. By the increase in intraabdominal pressure brought about by straining, the intravesical pressure is raised to between 60 and 100 cm. of water. Coughing raises the intravesical pressure to 70 cm. and sometimes even to 100 cm. of water (Roberts, 1953). In stress incontinence the amount of urine in the bladder is greatly reduced. Its capacity is often less than 100 ml. Involuntary expression of a few millilitres of urine takes place sometimes at a pressure as low as 15 to 30 cm. of water.

In the normal subject at rest (Figure II), the bladder neck as shown by cystourethrography lies 1 to 2 cm. behind the symphis pubis and 1 to 2 cm. above a line joining its lower border and the fifth sacral vertebra. The urethra is closed and joins the bladder at an angle of 100° posteriorly (Jeffcoate and Roberts, 1952). Under conditions of stress or increase in intraabdominal pressure, the bladder base and the proximal part of the urethra move downards and backwards to a limited extent, as these structures normally enjoy a certain amount of mobility. However, the shape of the urethra and its relation to the bladder are unchanged by stress (Jeffcoate and Roberts, 1952).

During the act of micturition the bladder outline becomes ovoid in shape and crenated posteriorly under the influence of detrusor muscle contraction. The internal urethral meatus rotates downwards and backwards to bring the trigone and the proximal part of the urethra into line, and at the same time the urethra dilates progressively from above downwards assuming a funnel shape. The distal third of the urethra remains fixed by its attachment to the urogetnital diaphragm forming an angle at this point, so directing the stream of urine downwards. When micturition is established the posterior urethro-vesical angle disappears completely, the urethra and the bladder base forming one and the same straight line. Towards the end of micturition the posterior urethro-vesical angle becomes partially restored, but the funnelling, though diminished, remains until the bladder sphincteric mechanism has regained its tone. The radiological appearances then revert to normal.

If by reason of modesty or other cause a woman fails to pass urine despite a genuine effort to do so, the detrusor contracts and the urethra dilates as far as the urogenital diaphragm, but no further. This is because the external voluntary sphincter is not relaxed (Roberts, 1953). In the same way, if a woman is asked to stop micturating before the bladder is empty, interruption of the stream

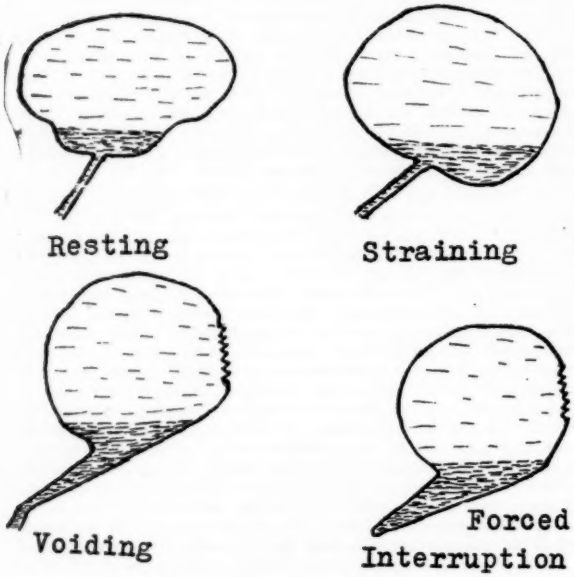

FIGURE II.

takes place at the level of the urogenital diaphragm, detrusor contraction and dilatation of the proximal part of the urethra persisting for an appreciable time thereafter. A similar finding was noted by Francis (1960) in 30 cases of acute post-operative retention of urine. The process of micturating was initiated normally in every case. The bladder detrusor contracted, the posterior urethro-vesical angle disappeared and the proximal urethra opened. However, the stream of fluid was always arrested at the level of the urogenital diaphragm. It would appear therefore that under normal circumstances the undamaged external voluntary sphincter can successfully withstand the effects of detrusor contraction.

A considerable departure from the normal is shown by cysto-urethrograms taken in cases of stress incontinence. However, these changes are by no means constant in all cases, nor do they occur together or to the same extent. Those most commonly seen are (Figure III) descent of the bladder neck with the patient resting in a sitting position, funnelling of the proximal half to two-thirds of the urethra with the patient straining, and loss of the posterior urethro-vesical angle with the patient straining and in severe cases even at rest.

Pathology.

The pathological lesion in stress incontinence would appear to be incompetence of the internal involuntary sphincter, resulting from developmental causes or disease of the nervous system, or, much more commonly, trauma at childbirth and in some cases operation; it is aggravated in many cases by post-menopausal atrophy of plain muscle fibres.

Discussion.

In the diamond-shaped area of the perineum or pelvic outlet there are two separate sphincters. In the anterior angle is the vesical sphincter and in the posterior angle the anal sphincter. That damage during childbirth is caused to the posterior or anal sphincter is well known. That similar damage is caused to the anterior or vesical sphincter is less generally appreciated. The anal sphincter is relatively strong and complex and consists of several parts. Damage to all but one of the separate parts can be sustained without incontinence. The damage which occurs is readily apparent by reason of laceration, and is repaired usually at once. The results are satisfactory enough to allow of reasonable continence. In the case of the vesical sphincters the damage is less readily recognized and is rarely if ever repaired as a primary procedure.

In the surgery of prolapse, except when previous operations have been performed, it is rare to find anatomical structures completely destroyed or missing. Although damaged and distorted, the structures are still present. Their intrinsic parts have been dislocated by descent of the fœtus and have healed in an abnormal position. It should be the object in operating for prolapse to find these structures, to free them and to restore them to their normal anatomical positions. To create artificial anatomy by the formation of slings and so on, or to unite structures which were never intended by nature to be united, is wrong in principle. Such operations will tend to fail and the abnormally opposed structures will tend to separate.

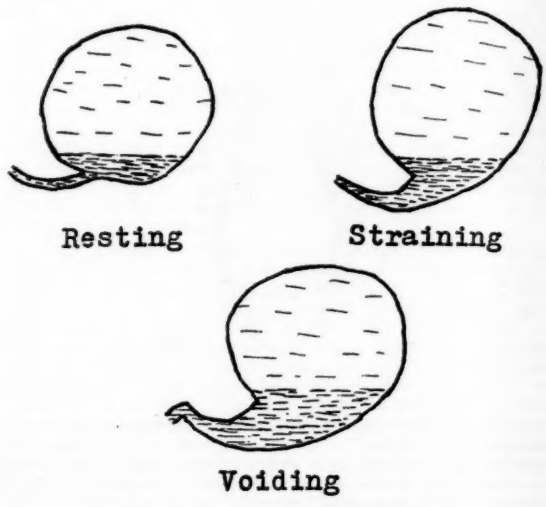

FIGURE III.

An operative technique aimed at the accurate correction of two of the major anatomical defects—namely, descent of the bladder neck and funnelling of the proximal urethra—was evolved by the writer. It was believed that in the process, correction of the third defect—namely, loss of the posterior urethro-vesical angle—would automatically follow and that normal bladder sphincteric control would be reestablished. So far this operation has been performed 117 times. The expectation has been fulfilled and the results have been eminently satisfactory.

Surgical Anatomy.

The surface anatomy of the anterior vaginal wall reveals a fold of skin directly beneath the external urinary meatus, the suburetheral fold, which is formed by the attachment of the vaginal skin to the triangular ligament, the inferior fascia of the uro-genital diaphragm or the perineal membrane. About an inch and a half above this is the transverse vaginal fold, lying at the level of the

vesico-urethral junction, which marks the fusion of the vaginal and vesical layers of endopelvic connective tissue to form the suburethral ligament of Wilfred Shaw. This forms the anterior and lowermost portion of a condensation of endopelvic connective tissue through which the urethra, surrounded by its distal sphincteric fibres, passes to the exterior. The anterior and uppermost portion consists of the medial and lateral pubo-vesical ligaments, which, though less well developed, are the homologues of the pubo-prostatic ligaments in the male. Medially this tissue occupies the anterior portion of the hiatus urogenitalis of the levatores ani or, in other words, the space which lies between the medial borders of the partes pubovaginalis, puborectalis and pubococcygeus of the levatores ani in that order from the medial to the lateral side. Laterally this tissue passes above the levator ani muscle and merges with its superior fascia to be attached to the endopelvic fascia in the region of the white line, which extends from the supero-posterior surface of the pubis to the spine of the ischium. The vesical sphincters surrounding the urethra lie within this endopelvic connective tissue and by merging with it laterally gain attachment on either side to the pubo-ischial rami of the pelvic bones.

Operation.

The incision is made in the mid-line of the anterior vaginal skin from the suburethral fold to a variable distance above the transverse vaginal fold, depending on the amount and type of cystocele present. It is carried through the suburethral ligament down to, but not through, the muscle fibres of the vesical sphincters surrounding the urethra. In the absence of scar tissue a line of cleavage is readily found. On either side the vaginal skin, with the suburethral ligament attached, is split from the remainder of the endopelvic connective tissue in this region as far laterally as the inferior pubo-ischial rami. This manœuvre will expose a large segment of the vesical sphincteric mechanism surrounding the urethra (Figure IV). Funnelling of the proximal half to two-thirds of the

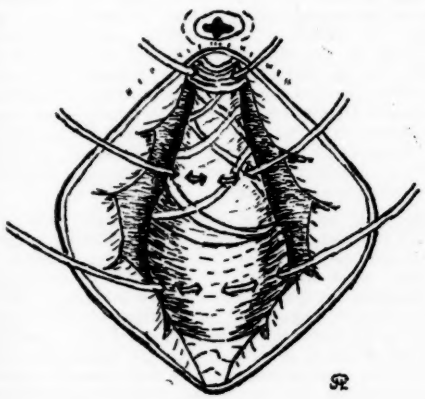

FIGURE IV.

urethra is readily seen and can be confirmed by the passage of an instrument, such as a Harris and Kripps hæmostatic forceps, into the lumen of the urethra and very gentle opening of the blades. When there is no stress incontinence and no funnelling of the urethra this appearance is not seen. When a urethrocele is present the urethra is more prominent and describes a curve of greater or less extent convex postero-inferiorly. In its lower half the wall of the urethra, surrounded by its sphincteric fibres, is very thin and delicate—about 2 mm. in thickness. In its upper half it becomes thicker and, when palpated over a urethral dilator, is raised up into an appreciable ridge from 3 to 5 mm. in thickness at the urethro-vesical junction. This is the main part of the involuntary sphincter.

With a fine, curved non-cutting needle threaded with number 000 or 0000 chromicized catgut, a series of five or six simple interrupted sutures are passed transversely and threaded in and out in such a manner that when these sutures (which at this stage are held with light hæmostatic forceps) are tied, the stretched and attenuated postero-inferior portion of the vesical sphincter will be ravelled up and its normal thickness restored. At the same time the funnelling of the urethra is obliterated and its lumen is restored to its normal cylindrical shape. Until some experience has been obtained with this method, and to avoid excessive narrowing, it is safer to tie the interrupted sutures over an instrument or catheter about the size of a number 19 urethral dilator. The sutures should be tightened just sufficiently to grip the instrument gently as it is moved up and down the urethra. One must take care not to enter the lumen of the urethra or, by tying the sutures too forcefully, to lacerate the sphincteric muscle fibres.

The urethra and the sphincteric mechanism are supported and the wound is closed by union and restoration of the endopelvic connective tissue, including the suburethral ligament with the vaginal skin attached by a single layer of number 0 chromicized catgut sutures from above downwards. The sutures are placed by means of a curved, non-cutting needle which, because it is easier and to avoid damage, is passed from within outwards (Figure V). The needle at first enters the relatively thick,

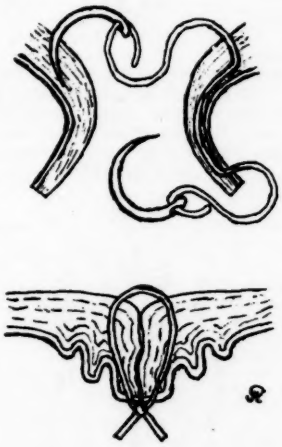

FIGURE V.

undamaged endopelvic connective tissue lateral to the urethra and then passes obliquely through the progressively thinning and stretched endopelvic connective tissue of the flap dissected from the urethrocele, to emerge through the vaginal skin a few millimetres from its cut edge (Figure VI). When these sutures are tied, either in series later or at the time, from above downwards, the effect is to draw together the stretched, separated and attenuated endopelvic connective tissue beneath and behind the urethra and to restore its normal thickened support. The attached vaginal skin in the process becomes furrowed, wrinkled and apparently redundant (Figure VII). As its surface area has not been increased, the rugæ merely having been flattened out, in principle it should not be removed (Loxton, 1955). In six weeks or so, when the healing process is complete, these folds will have largely subsided and the general appearance will have approached that of the normal.

Post-Operative Treatment.

The bladder is drained via the urethra by a narrow-gauge Foley's self-retaining catheter for five days or more, depending on circumstances and the mentality of the

patient. It is not necessary to pack the vagina with gauze, except when a more extensive colporrhaphy has been performed and when large flaps of vaginal skin and endopelvic connective tissue have been raised, leaving dead spaces in which blood and serum may collect. In the latter case packing has the additional effect of pressing the flaps down onto the underlying tissue as a full-thickness graft. The vaginal skin and subjacent tissue

FIGURE VI.

have a very rich blood supply, second only to that of the scalp and face. It is derived mainly from a lateral source through the hinges of these flaps. Sloughing, if it occurs at all, is of very limited extent and has never been a problem in these cases, even in the presence of infection.

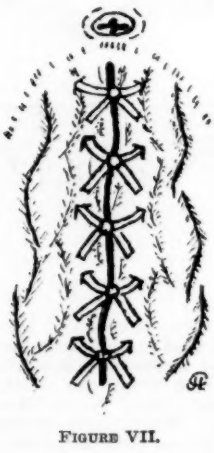

FIGURE VII.

This operation will stand up to the ordinary stresses and strains of the post-operative period. Early ambulation is encouraged from the outset. Unnecessary catheterization for residual urine should be avoided, as after this operation, if unskilfully carried out, it can be damaging. The patient is discharged from hospital as soon as normal bladder function is restored, which is about the eighth or tenth post-operative day. Thereafter the patient makes a gradual return to everyday life, intercourse being avoided until six weeks have elapsed since the operation.

Results.

So far 117 bladder sphincter repair operations have been performed by the writer. One hundred and four patients complained of stress incontinence and 102 have been found to be cured at a follow-up examination conducted at times varying from five years to three months after operation. In 13 of the 117 cases, although stress incontinence was not specifically complained of, at operation funnelling of the proximal half of the urethra was encountered. This was repaired as a prophylactic measure. From previous experience it had been found that a number of patients had developed stress incontinence soon after an otherwise satisfactory repair operation had been performed. Twenty-six patients suffered from persistent or recurrent stress incontinence after one or more attempts to deal with it by either the vaginal or the abdominal route. Of these 24 have been found to be cured after the operative procedure described in this paper. The two patients not so far cured both had persistent or recurrent stress incontinence. Both report substantial improvement.

One patient who did not succeed in emptying her bladder completely until 19 days after operation and was subjected to repeated catheterization (often six-hourly) developed a severe cystitis due to a mixed infection of antibiotic-resistant organisms. It is thought that repeated dilatation of the urethra and sphincter in the immediate post-operative period together with infection was responsible for failure in this case.

The other patient, who initially was completely incontinent at all times since a difficult confinement in 1954, recovered a certain amount of control after an anterior and posterior repair performed eight months later in May, 1955. Recurrence of prolapse of the anterior vaginal wall resulted in aggravation of the stress incontinence. This was treated in April, 1959, by a bladder sphincter repair. Much scar tissue was encountered in the suburethral region. Normal healing was impaired by sepsis and full continence was not reestablished. In September, 1960, a further attempt to repair the bladder sphincter was made. Although not completely successful, this has resulted in considerable recovery of urinary continence. Stress incontinence is now only slight, a few drops of urine being expelled under conditions of considerable stress. This patient is well satisfied with her condition. She states that she is much better than she has been during the past six years and is willing to submit to further operation if it is thought necessary.

In this series of 117 operations, the urethra was perforated by clumsy attempts at catheterization on four occasions, the catheter being forced posteriorly along the suture line in the direction of the vagina rather than anteriorly in the direction of the bladder. In two cases the urethra healed spontaneously under conditions of continuous catheter drainage of the bladder per urethram for 12 days. In the other two cases a urethro-vaginal fistula developed, which had to be closed by operation some three to four months later. All four of these patients are now completely continent.

In the case of two patients who developed a wound infection, complete dehiscence of the anterior vaginal wall occurred on absorption of the chromicized catgut sutures a few days after they left hospital. There had apparently been complete failure of the tissues to unite. Both these patients, though continent on leaving hospital, developed at once a recurrence of prolapse of the bladder neck associated with a severe degree of stress incontinence. One of these patients had not had stress incontinence before operation, and the other, though incontinent many years before, had been cured by a previous suburethral repair. Both these patients are now completely continent after a further vesical sphincter repair and anterior colporrhaphy.

Conclusion.

It is not claimed that the principles of this operation are new and original, but the method of putting them into effect may be. The technique is delicate; only the lightest of instruments are used. Success depends on meticulous attention to operative detail and accurate restoration of anatomy to the normal. By returning to primary principles, the whole problem of stress incontinence, which has become so complex, can be reduced to simplicity.

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Reviews.

Cardiac Problems: Papers Read at Three Symposia. London: The Chest and Heart Association. 7¾" × 4¾", pp. 144, with illustrations. Price: 18s. 6d., or $3.50.

IN this high-quality publication are presented 17 papers which made up the three annual symposia on cardiac problems first arranged by The Chest and Heart Association in 1958. Each symposium lasts only two and a half hours, so the papers of necessity are brief. The authors, despite their eminence in British cardiology, are frequently unable to fulfil satisfyingly their task of covering a big problem in a little time for a non-cardiological audience. Furthermore, the problems when they were presented were contemporary ones, and time has simplified or modified some of them. Consequently the inclusion of the 1958 series in a 1961 presentation tends to detract from the publication.

Despite this criticism, there is much to interest those who cannot keep in close touch with the rapid progress of modern cardiology. For example, the management of acute heart failure (Goodwin) is discussed in a clear and practical manner; the place of surgical treatment (Campbell) is clearly summarized; the diagnostic value of SGOT estimations (Gardner) is thoroughly set out; and the part played by endocrine adjustments in the development and management of cardiac œdema (MacKerson) is well presented.

These and other topics are dealt with in a general manner which requires no specialized knowledge. Through the wide field covered, this volume thus provides a bird's-eye view of the application of recent advances to the problems of clinical cardiology. On this understanding it can be recommended as a most useful book for the senior student and the general practitioner who needs a practical guide in this direction.

The Dyslipidoses. By Raûl Fleischmajer, M.D.; 1960. Springfield, Illinois: Charles C. Thomas Publisher, Oxford: Blackwell Scientific Publications Ltd. 9" × 6", pp. 528, with illustrations. Price: £6 8s. (English).

THE exact meaning of the term "dyslipidosis" may not be immediately apparent, and it is to be feared that reading this book will not necessarily answer the question. The

disorders which the author regards as dyslipidoses are classified by him in three main groups, hypercholesterolæmic, hyperlipæmic and normocholesterolæmic, each containing primary and secondary varieties. According to these criteria of blood lipid levels, "dyslipidosis" apparently encompasses a variegated mixture of conditions ranging from myxœdema through pancreatitis and gargoylism to histiocytosis X disease. It is a little difficult to understand how the much more important and prevalent condition of atherosclerosis escapes such a wide-flung net.

The conditions listed in the author's classification are each described in detail, and the chapters on familial hypercholesterolæmia, juvenile giant-cell granuloma and xanthoma disseminatum are particularly good. However, other sections are weak, and contain little of value beyond the descriptions of the dermatological lesions. These descriptions are good throughout the book. It is a pity that a less fanciful and more accurate title has not been found, since the present one is perhaps likely to disappoint the biochemically minded physician and to discourage the dermatologist, for both of whom this book does present information of value.

The Red Cell: An Account of its Chemical Physiology and Pathology. By T. A. J. Prankerd, M.D.; 1961. Oxford: Blackwell Scientific Publications. 8¾" × 5¾", pp. 194, with figures. Price: 32s. 6d. (English).

THE author of this book was an early investigator in the field of red-cell metabolism, and is well known for his publications on the metabolic defect in hereditary spherocytosis. The book ranges over some rapidly advancing fields in hæmatology with emphasis on red-cell metabolism and its abnormalities, the hæmoglobinopathies, hæmolytic mechanisms and problems of blood-bank storage. It is essentially a stock-taking of events of the past decade.

The monograph is presented as a series of reviews into various aspects of the red cell. Each chapter is well written and complete in itself. It is remarkable that so much material has been compressed into 169 pages of text. The reader who has previous knowledge of the subject will not be inconvenienced by the brevity of style and will enjoy the concise fashion in which difficult concepts are summarized. The more general reader may find some of the chapters rather heavy going and may wish for a more leisurely and detailed treatment. However, his path to wider reading is signposted adequately by a very complete bibliography.

This book makes apparent how much modern hæmatology is dependent upon the basic sciences. Recent advances have come especially from biochemists, geneticists and molecular biologists. The book should appeal to a wide circle of readers, and is highly recommended.

The Structure and Dynamics of the Human Mind. By Edoardo Weiss, M.D.; 1960. New York and London: Grune & Stratton. 8¼" × 5¼", pp. 496. Price: $8.75.

DR. EDOARDO WEISS has collected some of his more important papers in this book, the first of a proposed two volumes on the theory and practice of psychoanalysis. The work under review deals with the theoretical aspects of the discipline, and despite a little repetition, the separate papers, by modification and freshening-up in the light of more recent opinion, fit together as a fluent whole. The author is to be congratulated on his style, which is as lucid as the complex and highly technical material would allow.

The first section of the book presents a preliminary survey of mental structure. It is followed by a discussion of the ego and its relationship to the external world, including a résumé of the various theories of ego development. Dr. Weiss next discusses the id and the instincts, and includes an outstanding and very complete account of the various theories of instinctual drives which have been the source of much contention. He believes that the concept of a dichotomy of libidinal and aggressive drives is empirically useful, but remains unconvinced of the inherence of a "death instinct". The fourth and fifth sections concern the superego and the ego defence mechanisms. The last-mentioned is the weakest part of the book, being disappointingly incomplete in a work otherwise of high quality. The final section is a lucid exposition of the phenomena of dreaming.

Dr. Weiss is one of the most influential psychoanalysts in America today, and one of the few earlier members of the school still practising. He commenced his training-analysis in Vienna in 1909, having been referred to Paul Federn by Freud himself. Federn's loyalty to Freud prevented a schism between the two great teachers, and it was not until much later that the former felt free to present his contributions to theory with the emphasis they merited. He was among the first to insist on the centrality of the ego as a major focus for therapy, in contrast with the rather exhausted preoccupation with purely unconscious material then current. Dr. Weiss appears to have identified strongly with both the warm idealistic personality of his teacher and his theories, and has developed these in consonance with the emergence of ego-psychology after 1930.

This book should be of value to all who seek an up-to-date account of psychoanalytical theories, but because of the individual attitude towards certain metapsychological problems it can be recommended to the initiate only with reservations. The technical quality of the book is good, and the second volume, in which Dr. Weiss intends to deal with the psychopathology of neuroses and psychoses and to discuss classical and modified therapeutic techniques, is eagerly awaited.

Medical Entomology. By W. B. Herms, Sc.D., and revised by M. T. James, Ph.D.; fifth edition; 1961. New York: The Macmillan Company. 9¼" × 6", pp. 628, with illustrations. Price not stated.

SINCE the first edition of this book was published in 1915, there has been an enormous increase in our knowledge of arthropods and arthropod-borne diseases, which has gradually been incorporated in the text. The first and second editions were entitled "Medical and Veterinary Entomology", but subsequent editions were called "Medical Entomology", indicating the increasing difficulty of attempting to deal with both branches of the subject in one volume. Nevertheless, there is much of value to the veterinarian in the present edition.

While incorporating a great deal of new material, the reviser has managed to keep the size of the book down to about the same size as the fourth edition; indeed, there are slightly fewer pages. This has been achieved by omitting the general account of invertebrate parasites and some out-of-date sections. The valuable illustrations of arthropod morphology have been retained throughout, and the useful keys to genera and species retained or supplemented.

There are 21 chapters, each with a list of useful references. The insects dealt with include all those harmful to man. Classification, habits, relation to disease and control are discussed. Clinical notes are given, and the lesions produced by some biting arthropods are carefully described. Chapters are devoted to cockroaches and beetles, bugs, lice and gnats, including Simuliidæ, Psychodidæ and Ceratopogonidæ. Three chapters are given to mosquitoes, one dealing with their classification and biology, another with their rôle as vectors of disease, and the third with mosquito abatement. Other chapters deal with muscoid flies and louse flies, house flies, horse flies, tsetse flies and other blood-sucking muscoid flies, and on myiasis in general. Chapters are devoted to fleas, ticks, mites and pentastomids and venomous and urticarial arthropods, so that the term "entomology" has been broadly interpreted.

While the book is written primarily for North American workers, its scope is so wide and the fundamental aspects of morphological classification and control are so clearly set out that its value is world-wide. The general set-up is easy to follow, and the type is clear and legible. This book can be confidently recommended to clinicians as well as to laboratory workers.

Bedside Diagnosis. By Charles Seward, M.D., F.R.C.P. (Edin.), with a foreword by Lord Cohen of Birkenhead, M.D., D.Sc., LL.D., F.R.C.P., F.A.C.P., F.F.R.; Fifth Edition; 1960. Edinburgh and London: E. and S. Livingstone Ltd. 7¼" × 5", pp. 500, with illustrations. Price: 25s. (English).

THIS book is now appearing in its fifth edition. Much has been rewritten, and there are about 140 pages of new matter in it. There are 26 chapters in the book. "Psychogenic Symptoms" occupy the first chapter; then there are seven chapters on pain, anæmia, epistaxis, hæmatemesis, hæmaturia, hæmoptysis, hæmorrhagic disease, cough, dyspnœa, tachycardia, dysphagia, vomiting, diarrhœa, jaundice, debility and loss of weight, pyrexia, drugs causing symptoms, some uses of isotopes in diagnosis and, finally, normal values.

Before each chapter there is a convenient synopsis, which classifies the subject. The index is particularly helpful, providing quick and easy access to any desired information.

In the preface, the author remarks: "Clearly one who tries to be a General Physician with internal medicine as his field, is in the opposite state to that of the Specialist, in that he knows less and less about more and more." There is a tremendous amount of extremely useful, well-presented information to be found in this book, and it must be regarded almost as a classic of its kind, as Lord Cohen of Birkenhead remarks in the foreword:

> The student who masters the principle on which this handbook is based, will have an intelligent and rewarding approach to the diagnosis of disease, and he will have laid a foundation which will remain firm, whatever stress the superstructure of later knowledge may impose upon it, and even the experienced practitioner will learn much from its text.

Thymectomy for Myasthenia Gravis: A Record of Experiences at the Massachusetts General Hospital. By H. R. Viets, M.D., and R. S. Schwab, M.D.; 1960. Illinois: Charles C. Thomas; and Oxford: Blackwell Scientific Publications Ltd. 9" x 6", pp. 160. Price: 56s. (English), with illustrations.

IN this book the historical aspects, clinical features and medical management of myasthenia gravis are well covered, even if they are presented in a somewhat pedestrian style. The sections on clinical diagnosis, radiological features (diagnostic and therapeutic) and pathology are particularly well presented. The problems of pre-operative care, anæsthesia and surgical technique are presented in helpful detail.

In a book with six contributors, some duplication is inevitable, especially of the physiopathology of this disease. This does not detract seriously from its value. The problem of assessment of surgical results—a contentious matter over the years—is considered in detail; this is the only section in which a critical evaluation of the literature is attempted. By a quite pleasing juxtaposition, the conclusions of the authors are presented in the preface—which is best read after the main corpus. The typography and illustrations are beyond reproach.

Optics: An Introduction for Ophthalmologists. By K. N. Ogle, Ph.D.; 1961. Springfield, Illinois: Charles C. Thomas; Oxford: Blackwell Scientific Publications. 9" x 6", pp. 266, with figures. Price: 70s. (English).

THIS book can contain no new subject matter, but to its presentation the author brings much teaching experience and the resources of the Mayo Clinic. K. N. Ogle was formerly of the Dartmouth Institute, where he became interested in the basic principles underlying binocular vision. His papers and his previous book established his reputation in this field. Later he became a biophysicist to the Mayo Clinic, where he is an associate professor in the department of ophthalmology. Not only has he continued his own fundamental research, but he has initiated many young ophthalmologists into research disciplines.

The present book is based upon a series of lectures, laboratory demonstrations and discussions prepared for graduate students in ophthalmology, and so is presented to meet their needs. Light, mirrors, lenses, lens systems, instruments and ophthalmic optics are clearly explained, while the discussion of mathematics is kept to a minimum. The illustrations are particularly clear and instructive. Each chapter concludes with a number of exercises that can be used for practice in answering examination questions. The only regrettable feature is the price.

A Synopsis of Children's Diseases. By John Rendle-Short, M.A., M.D. (Cantab.), M.R.C.P., D.C.H.; third edition, 1961. Bristol: John Wright & Sons Ltd. 7¼" x 4¾", pp. 672. Price: 42s. (English).

THE author's objective in this book has been "to assemble all the relevant facts tidily for easy reference and rapid revision", in the hope that the book would be of value to undergraduates and post-graduates preparing for examinations. It will probably achieve this objective, and also provide a stimulus to further reading, especially as well-selected references are quoted. Essentials are well covered, it is, on the whole, well balanced, emphasis is placed upon common conditions, the text is clear, and the author has thoroughly sifted the material to be included. The information is up to date, and for those who like working from a synopsis, many fields of pædiatrics will be found well summarized in this book.

However, it is still a rather large book, and the insertion of brief comments on the rarer conditions makes parts rather disjointed. Since the book comes from a Sheffield background, it is surprising that the sections on child development and management of the normal child are so extremely brief. Much more could have been included upon behaviour patterns of infants and children at different ages, and the author purposely limits management of the normal child to brief comments on "rooming in", the causes of excessive crying and poor appetite in the young child. Sleep disturbances, a common problem, are not mentioned, and there are only 10 pages on psychological disorders. The section on lung infections is one of the least satisfactory, and could have been more clearly arranged. Bronchiolitis receives only two lines, and bronchiectasis eight pages. The section on accidents is inadequate, and more could have been written on prevention.

These, however, are minor criticisms. The book could prove most useful both to practitioners and to students, for on the whole, most of the information needed in the pædiatric field is included in considerable detail and with a common-sense approach.

Aerospace Medicine. Edited by Major-General Harry G. Armstrong, U.S.A.F. (Ret.); 1961. Baltimore: The Williams & Wilkins Company. 10" x 6¾", pp. 646 with illustrations. Price: £9 18s.

"ARMSTRONG" on aviation medicine has been a standard work since its first publication in 1939; indeed, for a number of years it was the only general text on aviation medicine in English. But the rate of change in this technology is so fast, especially since the race for space began four years ago, that the third edition of 1952 has become distinctly dated.

The range of subject matter has become wider, as the new term "aerospace" indicates, and General Armstrong has wisely shared the task of rewriting with 21 distinguished collaborators, all but one of them associated with the United States Air Force. Their product is virtually a new book. Although the book is intended to examine in detail the medical problems of both civil and military aviation and astronautics, the emphasis is on military aviation. Civil aviation has one chapter and space flight has two chapters. There are few references to other than the American literature.

Of the 32 chapters, eight are devoted to the aviation medical examination, some topics being traversed by two authors. There is also a chapter on methods of psychological selection for military flying. Aspects of altitude—hypoxia, decompression sickness, aerotitis and protective equipment—occupy six chapters and effects of acceleration another four. Other environmental stresses, with the exception of microwave and nuclear radiations, are well covered, and the chapter on escape and survival is excellent.

There are some curious omissions, perhaps the result of the multiple authorship. Thus linear acceleration and accidents are both discussed at some length, but little is said about protective equipment or crash protective design, nor are the remarkable advances in aviation pathology dealt with, although the Joint Committee on Aviation Pathology is mentioned in the chapter devoted to toxicology.

Notwithstanding these criticisms, the book is generally successful as a comprehensive treatise. The printing and illustrations are clear, misprints are few, and the index is adequate. It can be recommended to all service medical officers whose duties relate to flying, and to civil aviation medical examiners.

Scientific Aspects of Neurology. Edited by Hugh Garland, T.D., M.D., F.R.C.P.; 1961. Edinburgh, London: E. & S. Livingstone Ltd. 9¼" x 6", pp. 274, with illustrations. Price: 50s. net.

THE editor states in the preface to this book that in Leeds in 1959-1960 he arranged a weekly series of post-graduate lectures covering aspects of the whole field of the neurological sciences. The lectures proved popular and it was decided to publish most of them as a book. This was not intended to be a work on recent advances or modern trends in neurology; the views expressed, while modern, were not necessarily recent.

Nineteen of the 20 contributors are from Great Britain; of these seven are neurologists, three neurosurgeons, two pathologists and two physiologists; the five others deal with problems of psychiatry, chemical pathology, experimental psychology, neuroradiology, and pharmacology respectively. Five are from Leeds and the rest from other parts of Britain; Dr. Ludo van Bogaert, who writes about disseminated sclerosis, is the distinguished foreign partici-

pant. The names of the contributors and their topics suggest that the editor meant the course to include much more than the fundamental sciences, and so it proves; perhaps "Scientific and Clinical Aspects of Neurology" would have been a better title for the book. Yet, when its contents are examined, it is found that both aspects have been largely integrated, not only in the book as a whole, but also in almost every article. This successful integration stamps the book with a quality that is enhanced by adequate references and some very good illustrations; the type and the arrangement are extremely clear.

It would be unfair specially to notice any one article because of its importance or excellence, for all are important and good. However, the editor and his collaborators would—we are sure—approve of our making an exception and citing the late Sir Geoffrey Jefferson's account, based on his vast experience, of the physiology of sleep and its practical application as an admirable illustration of what has been said. Other acknowledged authorities present their subject is an equally admirable manner; for instance, Sir Francis Walshe, in the opening chapter, gives us the fruits of his long and untiring study of the origin of the pyramidal tract.

In conclusion, it may fairly be stated that the decision to publish these lectures was well grounded; they deserved to be disseminated beyond their place of origin. Even if the solution of some of the problems is scarcely in sight, we are glad that those who wrestled with them did not receive the advice (or heed it if given) which Horace (*Ars Poetica*, 388-389) gave to the would-be poet:

Nonumque prematur in annum,
Membranis intus positis.

Books Received.

[The mention of a book in this column does not imply that no review will appear in a subsequent issue.]

"The Dismissal: The Last Days of Ferdinand Sauerbruch Surgeon", by Jürgen Thorwald; 1961. London: Thames and Hudson Ltd. 8½" × 5½", pp. 256, with 27 halftone illustrations. Price: 21s.

"Textbook of Physiology and Biochemistry", by George H. Bell, B.Sc., M.D., F.R.F.P.S.G., F.R.S.E., J. Norman Davidson, M.D., D.Sc., F.R.F.P.S.G., F.R.I.C., F.R.S., and Harold Scarborough, M.B., Ph.D., F.R.C.P.E., F.R.C.P.; fifth edition; 1961. Edinburgh and London: E. & S. Livingstone Ltd. 9¼" × 6¼", pp. 1126, with many illustrations. Price: 70s

"The Kidney: An Outline of Normal and Abnormal Structure and Function", by H. E. de Wardener, M.B.E., M.D., F.R.C.P.; second edition; 1961. London: J. & A. Churchill Ltd. 9¼" × 6", pp. 382, with 88 illustrations. Price: 50s.

"Williams: Obstetrics", by Nicholas J. Eastman and Louis M. Hellman; twelfth edition; 1961. New York: Appleton-Century Crofts, Inc. 9¾" × 6¼", pp. 1205, with 666 illustrations. Price: $16.00.

"Blacklock and Southwell: A Guide to Human Parasitology: For Medical Practitioners", revised by T. H. Davey, O.B.E., M.D. (Belfast), D.T.M. (Liverpool); seventh edition; 1961. London: H. K. Lewis and Co. Ltd. 9¾" × 6", pp. 232, with 122 illustrations. Price: £1 10s.

"The Making of a Surgeon", by Ian Aird; 1961. London: Butterworth and Co. (Publishers) Ltd. 8½" × 5½", pp. 150. Price not stated.

"Modern Contraception: A Practical Guide to Scientific Birth Control", by Philip M. Bloom, M.B., Ch.B., D.G.O., L.M.; 1961. London: Delisle Limited. Sydney: Specialist Publications. 7" × 5", pp. 48, with illustrations. Price: 3s. 6d.

"Current Problems in Electrobiology", *Annals of the New York Academy of Sciences*, Volume 94, Art. 2; Conference Editor, Dominick P. Purpura; edited by Franklin N. Furness; 1961. New York: The New York Academy of Sciences. 9" × 6", pp. 318, with many illustrations. Price not stated.

"David Edwardes: Introduction to Anatomy 1532: A Facsimile Reproduction with English Translation and an Introductory Essay on Anatomical Studies in Tudor England", by C. D. O'Malley and K. F. Russell; 1961. London: Oxford University Press. 8½" × 5½", pp. 64. Price: 28s.

"The Medical Annual: A Year Book of Treatment and Practitioner's Index", edited by R. Bodley Scott, M.A., D.M., F.R.C.P., and R. Milnes Walker, M.S. (London), F.R.C.S.; seventy-ninth year; 1961. Bristol: John Wright and Sons Ltd. 8½" × 5½", pp. 664, with illustrations. Price not stated.

"The Surgical Clinics of North America: Difficult Diagnostic Problems in Surgery", Mayo Clinic Number, Volume 41, number 4, 1961. Philadelphia and London: W. B. Saunders Company. 9" × 5¾", pp. 1140, with illustrations. Price: Bi-monthly £8 2s. 6d., yearly, paper £6 15s.

"Clinical Obstetrics and Gynecology", Volume 4, number 3: "Cardiovascular-Renal Problems in Pregnancy", edited by Russell R. De Alvarez, M.D. "Ovarian Tumours", edited by Langdon Parsons, M.D.; 1961. New York: Paul B. Hoeber Inc. 9¼" × 6", pp. 316, with illustrations. Price: $18 per annum.

"An Introduction to Anæsthetics: For Medical Students and House Officers", by John D. Laycock, M.B., B.S. (London), F.F.A.R.C.S.; 1961. London: Lloyd-Luke (Medical Books) Ltd. 7¼" × 5", pp. 132. Price: 10s.

"The Nature of Essential Hypertension", by George Pickering, M.D., F.R.C.P., F.R.S.; 1961. London: J. & A. Churchill Ltd. 8" × 5¼", pp. 160, with 58 illustrations. Price: 22s. 6d.

"Neoplastic Disease at Various Sites: Volume IV. Tumours of the Œsophagus", edited by Norman C. Tanner, M.D., F.R.C.S., and D. W. Smithers, M.D., F.R.C.P., F.F.R.; 1961. Edinburgh and London: E. & S. Livingstone Ltd. 9¾" × 6½", pp. 364, with many illustrations. Price: 63s.

"Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest", by H. Gobind Khorana; 1961. New York: John Wiley and Sons, Inc. 9" × 6", pp. 152, with illustrations. Price: $5.25.

"Standard Nomenclature of Diseases and Operations", edited by Edward T. Thompson, M.D., F.A.C.H.A. and Adaline C. Hayden, C.R.L.; fifth edition; 1961. New York, Toronto, London: McGraw-Hill Book Company Inc. 8½" × 5½", pp. 980. Price not stated.

"The Story of X-Rays from Röntgen to Isotopes", by Alan Ralph Bleich, B.A., M.D.; 1961. New York: Dover Publications Inc. 8" × 5¼", pp. 186, with many illustrations. Price: $1.35.

"Chemotherapy of Tuberculosis", by William F. Russell, Jr., M.D., M.S., and Gardner Middlebrook, M.D.; 1961. Illinois: Charles C. Thomas, Publisher. 9" × 6", pp. 144, with illustrations. Price: 52s.

"Bioelectricity", by E. E. Suckling, D.E.E.; 1961. New York, Toronto, London: McGraw-Hill Book Company Inc. 8" × 5½", pp. 244, with 92 illustrations. Price: $8.75.

"Development and Structure of the Cardiovascular System", edited by Aldo A. Luisada, M.D.; 1961. New York, Toronto, London: McGraw-Hill Book Company Inc. 10" × 6¾", pp. 234, with 100 illustrations. Price: $9.95.

"Malformations of the Face", by D. Greer Walker, M.A., M.D., B.Ch., M.Dent.Sc., F.D.S.R.C.S.; 1961. Edinburgh and London: E. & S. Livingstone Ltd. 9¾" × 6¾", pp. 214, with 93 illustrations. Price: 37s. 6d.

"Psychopathology of Aging: The Proceedings of the Fiftieth Annual Meeting of the American Psychopathological Association, Held in New York City, February, 1960", edited by Paul H. Hoch, M.D., and Joseph Zubin, Ph.D.; 1961. New York, London: Grune & Stratton Inc. 8½" × 5¼", pp. 336, with illustrations. Price: $9.75.

"Chemical Pathology of the Nervous System: Proceedings of the Third International Neurochemical Symposium, Strasbourg, 1958", edited by Jordi Folch-Pi; 1961. Oxford, London, New York, Paris: Pergamon Press. 9¾" × 6¼", pp. 896, with illustrations. Price: £7.

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"The Myocardium—Its Biochemistry and Biophysics", edited by Alfred P. Fishman, M.D.; 1961. New York: New York Heart Association Inc. 10¾" × 8", pp. 228, with illustrations. Price not stated.

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ASYLUM TO COMMUNITY.

DEVELOPMENTS in the care of the mentally ill in Victoria, together with the provision of an increasing number of community services directed towards the same end, have, since 1952, when the Victorian Mental Hygiene Authority was first appointed, aroused considerable interest among psychiatrists throughout Australia. At the request of the World Federation for Mental Health and with this organization's financial support the Authority's Chairman, Dr. E. Cunningham Dax, has now written an account of these developments.[1] These, as Dr. J. R. Rees, Director of the Federation, has stated, should be of interest not only to psychiatrists but to administrators and those members of the general public who are concerned as to the measures necessary to combat the growing socio-medical problems of mental illness. No attempt has been made to dramatize this account, which for the most part adheres strictly to matters of fact. Nevertheless, drama is contained within the pages of this book, for it is undoubtedly a success story.

If Dr. Dax's work is read in conjunction with the recent report of the Royal Commissioner on Callan Park Mental Hospital, some interesting contrasts and comparisons can be made. It is clear that conditions at Kew Mental Hospital in 1952 and before were by no means dissimilar to some of those which can currently be found in Callan Park. Dr. Dax's book includes photographs of a toilet, dormitory and other facilities as they were when the Mental Hygiene Authority first took over. The Royal Commissioner has done the same in his report and the similarity between the two sets of photographs is such that they could be interchanged without exciting comment.

One cogent observation made is that where poor conditions do exist, there is no sense in attempting concealment. The importance of this principle has clearly escaped some administrators elsewhere, who not only do attempt to conceal what is unsatisfactory, but are constantly watchful and defensive against any attempted exposure. In doing so they are likely to make rods for their own backs with which they will surely be beaten sooner or later. Furthermore, such attitudes defeat much-needed public interest—the moral being that the problems of mental illness are far too large to be left entirely in the hands of governments alone.

Dr. Dax has some interesting advice to give those who, it may be hoped, will sooner or later emulate his example. Discussing the development of community services, he points out that where so much needs to be done, no service should be introduced until the public, the professions and those working in the social services see and feel the need for its inception. He also emphasizes how unsatisfactory and restrictive legislation can hamper the growth of a new service. This was certainly true, for example, in New South Wales, where no substantial improvement in psychiatric services began to occur until after the introduction of the new *Mental Health Act* of 1948.

Dr. Dax's views on the future of mental hospitals are a subject for discussion. He is of the opinion that existing mental hospitals, at least as an interim measure, might be regarded as units for the future care of geriatric patients and for the training of the intellectually defective. This may be satisfactory except inasmuch as interim measures have a way of acquiring permanency. Many also are of the opinion that the geriatric problem could be better solved in other ways than by caring for the aged in large institutions. In many cases some less impersonal, more domiciliary kind of accommodation is to be preferred. So, too, with the intellectually handicapped, who (except for cot cases obviously needing hospital care) may, given the necessary facilities for special training and education, be better looked after either on a day basis or in hostels rather than in hospital-type accommodation. However, no serious criticism is implied; from the point of view of practical economics, existing accommodation cannot be allowed to remain unoccupied, though the problem of how best to use this is still outstanding.

By adopting a definite policy of development and by giving attention to the need for careful planning, Dr. Dax and his co-workers have achieved a very great deal in a very short time. Special attention has also been given to the morale of staff, with the result that the Victorian Mental Hygiene Department has a better staff-patient ratio than any other in Australia. As is correctly stated, although the living standards and status of patients are matters of great importance, their welfare and ultimate rehabilitation are more dependent on the staff's understanding, attitude and training than on any other factors. Apart from hospitals, Victoria's growing community mental health service should rightly be a matter for envy by all the other Australian States. If this is what a competent Mental Hygiene Authority can accomplish, then those responsible for the improvement of mental health services elsewhere could do no better than to follow closely, and as speedily as possible, Victoria's lead.

[1] "Asylum to Community: The Development of the Mental Hygiene Service in Victoria, Australia", by E. Cunningham Dax; 1961. Melbourne, Canberra, Sydney: F. W. Cheshire. 8½" × 5½", pp. 230, with illustrations. Price: 30s.

THE NEWER RESPIRATORY VIRUSES.

OVER the past decade many new respiratory viruses have been isolated. This is the result of applying tissue culture techniques to specimens from patients with respiratory diseases. It is likely that these are "newly-

discovered" viruses, rather than new species which have suddenly appeared in our communities.

Adenoviruses were first demonstrated in 1953 by W. P. Rowe *et alii*[1] and subsequently shown to comprise a large group of viruses which share a common antigen. In 1956 R. M. Chanock[2] described the hæmadsorption viruses which were later reclassified by C. H. Andrews *et alii*[3] as the *Myxovirus parainfluenzæ* group. Also in 1956, J. A. Morris *et alii*[4] recovered the agent now known as the respiratory syncytial virus. Certain of the enteroviruses also appear to be ætiologically concerned in minor respiratory disease. These include the ECHO 10 group, for which the name "reovirus" was proposed by A. B. Sabin,[5] the JH viruses described by J. H. Price[6] and now called ECHO 28, and the Coe virus described by E. H. Lennette *et alii*[7] and now regarded as an enterovirus. During 1960 D. A. J. Tyrrell and R. Parsons[8] from Salisbury, and D. Hobson and G. C. Schild[9] from Sheffield in England have reported isolation of "common cold" viruses with successful reproduction of coryzal symptoms in human volunteers.

The advent of many new viruses over a short period of time is somewhat bewildering to the practising physician, especially so because a simple concept has prevailed. When a respiratory illness is toxic and prostrating, it has been classed as "influenza", but when the illness is truly minor in nature it has been labelled a "cold". A clearer picture of the epidemiology of minor respiratory disease is slowly emerging. Many respiratory illnesses, which are commoner in childhood than in adult life, are caused by these "newer" viruses as well as by *Myxovirus influenzæ*. Some, such as adenovirus type 5, are endemic, but most viruses appear in epidemic form and at irregular intervals of time. What appear to be recurring winter epidemics of the same minor respiratory illness are usually separate and distinct epidemics due to different viral agents which all produce an apparently identical clinical picture.

Major respiratory illness, such as pneumonia, arises as a result of secondary bacterial infection in a minor respiratory disease and may, therefore, show the same epidemic pattern as the current minor disease. This is demonstrated by the increased numbers of hospital beds required to nurse patients with pneumonia when influenza is epidemic, as shown by J. A. Forbes.[10] The bacterial pathogen concerned in these epidemics of pneumonia will vary according to the prevailing pharyngeal flora in the community involved, but, if specimens are examined prior to antibiotic therapy, it is found that pneumococci are still the commonest bacterial agent.

It is seldom possible, with any pretence at accuracy, to distinguish one respiratory illness from another on clinical grounds, but there are two exceptions, and there is hope that greater familiarity with the patterns of disease caused by other viruses may further clarify the position. Croup, or laryngo-tracheo-bronchitis, is a characteristic clinical syndrome in infants and young children, and it has been found, as shown by F. A. Lewis, Noreen I. Lehmann and A. A. Ferris in a paper in this issue (see page 929), that the majority of patients are infected with one of the hæmadsorption or *Myxovirus parainfluenzæ* viruses. Epidemic bronchiolitis is another clinical entity familiar to most pædiatricians. According to an editorial article in the *British Medical Journal*,[11] the term bronchiolitis covers conditions which have been named capillary bronchitis, epidemic bronchopneumonia, virus pneumonia and asthmatic bronchitis, and the syndrome is mostly seen in children under the age of two years, especially in those under the age of six months. As discussed by Lewis, Lehmann, Ferris and Margery L. Rae, in another article in this issue (see page 932), respiratory syncytial virus is ætiologically related to epidemic bronchiolitis in young children. There are, therefore, at least two groups of respiratory virus which produce recognizable syndromes in infants and young children. It seems that a clinical diagnosis of croup or bronchiolitis in young children may carry with it the certain knowledge of its ætiology. Unfortunately, the position in older children and adults is less clear because disease syndromes which follow infection with the same viral agent are nondescript in nature.

Our understanding of the epidemiology of respiratory disease is merely fragmentary, although progress has been made. Many serological types of virus are known, but it is likely that there are many more yet to be discovered. Already it is apparent that development of a vaccine which might confer immunity to the common respiratory illnesses is no easy matter. There are problems involved in having the right viruses in a vaccine as well as problems in administration and duration of immunity. Whereas certain diseases, such as influenza, are susceptible to attack, it seems unlikely that the over-all incidence of respiratory disease will be substantially reduced in the near future by the use of polyvalent vaccines.

[1] *Proc. Soc. exp. Biol. (N.Y.)*, 1953, 84:570.
[2] *J. exp. Med.*, 1956, 104:555.
[3] *Virology*, 1959, 8:129.
[4] *Proc. Soc. exp. Biol. (N.Y.)*, 1956, 92:544.
[5] *Science*, 1959, 130:1387.
[6] *Proc. nat. Acad. Sci. (Wash.)*, 1956, 42:892.
[7] *Amer. J. Hyg.*, 1958, 68:272.
[8] *Lancet*, 1960, 1:239.
[9] *Brit. med. J.*, 1960, 2:1414.
[10] MED. J. AUST., 1958, 2:75.

Comments and Abstracts.

THE BASIC MEDICAL SCIENCES IN THE MEDICAL CURRICULUM.

ALMOST continuous debate centres around the place of the basic medical sciences in the medical curriculum. The rapid expansion of knowledge in these spheres must force increasing selection in the amount of them which is to be taught, or perhaps rather the amount that a student is to be expected to know, and constant thought needs to be given to their coordination into the over-all programme of educating the medical student. The emphasis of a recent report of a WHO expert committee[1] is on showing how the medical student can be given a more balanced

[11] *Brit. med. J.*, 1960, 2:1863.

[1] "The Teaching of the Basic Medical Sciences in the Light of 'Modern Medicine': Eighth Report of the Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel", World Health Organization Technical Report Series No. 209; 1961. Geneva: World Health Organization. 9½" × 6¼", pp. 31. Price: 1s. 9d. (English).

outlook by taking advantage of the many opportunities that arise for emphasizing preventive aspects of medicine in teaching the basic medical sciences. The committee, under the chairmanship of Professor W. J. Hamilton, Professor of Anatomy in the University of London and Dean of the Charing Cross Hospital Medical School, met in Geneva in August, 1960. Its report recognizes that the inculcation of an outlook orientated to the preventive aspects of medicine will not be easy, for, it is said, every student enters medicine with a preconceived belief that the care and treatment of sick people are his primary tasks. The report suggests that, since too little attention is given to the preventive aspects of medicine in existing textbooks, a new one should be prepared written from the standpoint of "Man, his life and environment", and emphasizing the many aspects of preventive medicine to which attention has been drawn in recent years.

The committee is of the opinion that before entering medical school the student should already have received a good grounding in physics, chemistry and biology. It emphasizes the need to modernize the teaching of biology, which can form a valuable introduction to the student's later studies in pathology and histology, and suggests that botany, which has undoubtedly declined in importance in relation to the medical curriculum, could be used to provide an introduction to methods of evaluating the results of clinical trials and opportunities for learning the principles of carrying out epidemiological surveys. Laboratory studies on plants are said to provide in a very simple, cheap and humanitarian way a particularly good introduction to that distinctively biological scientific method the "controlled experiment". Further, the results of such experiments can be expressed in quantitative terms, so that observations made by the students, both individually and collectively, are admirably suited to give practical instruction in some of the simpler and more dependable statistical techniques. The students have the added incentive of using their own data for these purposes, and what may begin as a mere laboratory exercise may well end in a piece of simple but constructive research.

More than half the report is devoted to an analysis of the subject matter to be included in the pre-clinical course and the manner in which it should be taught. The committee states that the growing importance of radiation medicine makes it imperative that the medical student should be familiar with the properties of ionizing radiations, their applications, and the precautions that can be taken to prevent injurious exposure. The teaching of physiology offers considerable scope for the discarding of traditional material to make way for certain more recent developments, such as ergonomics, sociophysiology and psychophysiology. The aim, it is stated, must be to give the student a clear understanding of the range of responses of which the human organism is capable under diverse environmental conditions, for it is on a knowledge of the possibilities and limitations of homœostasis that specific preventive measures must ultimately be based. A sound training in biochemistry is obviously a necessary prerequisite for instruction in bacteriology, virology, pharmacology, pathology and other branches of medical science, and here, too, the committee considers that there are opportunities for illustrating the preventive side of medicine, such as the elimination of deficiency diseases or the correction of metabolic defects.

The fundamental aspects of genetics should, in the opinion of the committee, have been covered before the student enters medical school, but where this is not possible instruction should be started early in the preclinical period. In the later part of this period, the committee states, some instruction in cytogenetics can be given, but it is thought advisable that the teaching of human genetics should be postponed until the end of the clinical period. The report further underlines the importance of adequate instruction in medical psychology, recommending that it should be taught as the product of medical experience, with emphasis on the patient-doctor relationship and the psycho-sociological consequences of disease. Finally the report discusses briefly the teaching of pathology and microbiology in the light of the preventive approach to medicine.

A concluding section in the report, under the heading "Areas of Contact", sums up the importance of collaborative teaching between the various departments of a medical school. The committee states that an entire curriculum should be so organized that the medical student obtains the greatest benefit, not only for medical practice, but also for his education in the scientific and humanistic aspects of medicine. The procedures for affecting such continued and coordinated teaching will vary with the organization of the medical school and particularly with the personalities of the teachers. Fields of interest common to the basic medical subjects should be exploited to emphasize the interdependence that exists among modern medical sciences; the clinical pathological conference in which teachers of the basic sciences also participate has been found a particularly fertile field for such cooperation. No modern medical science progresses by itself, the report points out; advances in one subject lead to advances in all. "While the student must be trained in the constituent subjects of human biology and learn his fundamentals from experts in the various disciplines he should also be made aware of the fact that his final goal is a concept of the whole man and the influence his environment exerts upon him. The functions of medical schools are to provide such educational opportunities, and to imbue doctors with a sense of their duty to society." Believing in the importance of teaching preventive medicine in the basic sciences as a means of developing an awareness of such social responsibilities, the committee has very rightly emphasized this aspect of medical education throughout the report.

CLINICALLY UNRECOGNIZED MYOCARDIAL INFARCTION FOLLOWING SURGERY.

MYOCARDIAL INFARCTION may occur during surgery or in the post-operative period. The usual clinical picture of infarction in the early post-operative period may be obscured by such factors as sedatives, incisional pain, and respiratory or gastro-intestinal complications. Objective findings often found in myocardial infarction, such as fever, leucocytosis, increased blood sedimentation rate and a rise in the serum level of glutamic oxalacetic transaminase, are of uncertain value after surgical trauma. The electrocardiogram, therefore, may provide the only evidence of acute myocardial infarction in the early post-operative period. Mendelsohn and Monheit[1] recorded electrocardiograms before and after operation in 50 patients submitted to upper abdominal surgery, and found that four had electrocardiographic changes of myocardial infarction post-operatively without any symptoms or suggestive signs. These authors suggested that the incidence of myocardial infarction following surgery might be considerably higher than was suspected.

A much more extensive survey along these lines has been recently published by A. C. Driscoll, J. H. Hobika, B. E. Etsten and S. Proger.[2] A random sample was taken of patients submitted to all types of surgery. Such sampling was performed by selecting for study the first three patients to enter the operating theatre on Tuesday, Wednesday and Thursday of each week. A total of 496 patients was studied. Pre-operative electrocardiograms were taken before surgery in each case, and in the first 150 of the series the tracings were repeated 6, 24 and 72 hours after surgery. It was then appreciated that no significant change in the electrocardiogram occurred at six hours which did not persist for 24 hours, so the last 346 patients had tracings performed routinely only 24 hours after operation. Subsequent tracings were taken if there were any significant changes found in the 24-hour trace.

Myocardial infarction occurred in 12 of the unselected 496 patients, an incidence of 2·4%. Only two of the 12

[1] *New Engl. J. Med.*, 1956, 254: 307 (February 16).
[2] *New Engl. J. Med.*, 1961, 264: 633 (March 30).

patients had chest pain typical of myocardial infarction. Four other patients might have been suspected of having an infarction on clinical grounds—three had persistent hypotension and one had respiratory distress. In the remaining six, post-operative myocardial infarction was completely unsuspected on clinical grounds. The electrocardiograms in 11 of these patients were diagnostic of infarction. The diagnosis in the twelfth patient was made at autopsy—there was left bundle branch block present before and after surgery, and there were no diagnostic changes in the electrocardiogram. One other of these 12 patients also died from his infarction; the other 10 made an uneventful recovery.

All the post-operative myocardial infarctions occurred in patients over 50 years of age, of whom there was a total of 271. Hence the incidence in patients over 50 was 4·5%. Furthermore, all the patients in whom myocardial infarction occurred had one or more of the following conditions present pre-operatively: known chronic ischæmic heart disease, systemic hypertension, diabetes mellitus, peripheral vascular disease, or an abnormal electrocardiogram. Since 167 of the 271 patients over the age of 50 years had one or more of these conditions, the incidence of post-operative myocardial infarction in this group was 7·2%.

In addition to the 12 patients with definite electrocardiographic evidence of myocardial infarction, there were 30 who had electrocardiographic changes which were significant, but which were not diagnostic of infarction. The authors could not attribute these changes to any extracardiac factor. All these patients had inversion of the *T* waves in one or more leads, and in three it was associated with some *ST*-segment depression. These changes were transient and in most cases disappeared within a week. It is, of course, well known that transient *T*-wave changes can occur with normal hearts. This was very adequately pointed out in this journal in 1958 by Seldon,[3] who emphasized its innocent nature. It is of interest therefore to note that Driscoll *et alii* have some evidence that transient *T*-wave inversion occurring post-operatively may be related to ischæmic heart disease. They point out that if these changes were unrelated to coronary heart disease, there should have been a comparable incidence of such changes in patients without the factors favouring the development of coronary atherosclerosis. But this was not the case in this group of 30 patients. Nine of the patients had no such factors, whereas 21 did have one or more of the five pre-operative conditions common to the 12 patients in whom definite myocardial infarction developed—namely, known ischæmic heart disease, hypertension, diabetes mellitus, peripheral vascular disease or an abnormal electrocardiogram pre-operatively.

The conclusion to be drawn from this study is that it is highly desirable to evaluate carefully the cardiovascular status of patients over the age of 50 years who are submitted to surgery. Ideally, an electrocardiogram should be part of the pre-operative "work-up". In any case, an electrocardiogram would appear to be essential pre-operatively and post-operatively in patients with any of the five conditions already mentioned which are commonly associated with ischæmic heart disease. The comparatively high incidence of "silent" myocardial infarction in this group is adequate justification for the carrying out of this simple procedure. However, it should be emphasized that there are numerous extracardiac factors which may make the interpretation of post-operative electrocardiograms difficult. For example, significant changes may occur with electrolytic disturbances, abdominal distension, atelectasis and pleural effusion. With a strongly suggestive clinical picture, it is justifiable to diagnose myocardial infarction on the basis of comparatively few electrocardiographic changes. But "silent" post-operative infarction should never be diagnosed unless the electrocardiogram shows the classical pattern of a *Q* wave with *ST-T* changes, or else persistent deeply inverted *T* waves.

[3] MED. J. AUST., 1958, 2:154 (August 2).

SHORTER ABSTRACTS.

OPHTHALMOLOGY.

UVEITIS AND URO-GENITAL DISEASE IN THE MALE. R. D. Catterall and E. S. Perkins, *Brit. J. Ophthal.*, February, 1961.

THE authors examined 226 consecutive male patients attending the uveitis clinic of the Institute of Ophthalmology. Four had non-inflammatory lesions, and none of these had prostatitis. Eleven were diagnosed as suffering from Eale's disease, and only one of these had chronic prostatitis. The remaining 211 patients had uveitis, and of these 145 were found to have chronic prostatitis. The incidence of prostatitis was higher in patients with anterior uveitis, and of these 28·6% had Reiter's disease and 18·8% had ankylosing spondylitis. The authors suggest that acute anterior uveitis in the male cannot be considered as an isolated disease entity, but is closely linked with disorders of other mesodermal constituents of the body.

THE USE OF ^{32}P IN THE DIAGNOSIS OF OCULAR TUMOURS. B. Goldberg *et alii*, *Arch. Ophthal.*, February, 1961.

THE authors present their experiences in the use of radiophosphorus in 125 cases of suspected tumour. The radioactive phosphorus was administered intravenously in a dose of 350 to 500 μc of ^{32}P. Counts of activity over the lesion and control sites were performed initially in the series at 1 and 24 hours and later at 48 hours. For posterior segment lesions a transconjunctival approach was necessary, and in these cases the count was restricted to 48 hours. In this series 92 cases were studies by the external approach and 33 by the transconjunctival approach. In 37 the results were positive, in 66 negative and in 22 equivocal. Of the 37 positive results two were "false positives", and the presence of malignant tumour was confirmed pathologically in 30. The remaining five patients refused enucleation. The authors stress the importance of an accurate history, the necessity of positioning the probe on the sclera directly over the lesion, the use of the transconjunctival approach to study a posterior choroidal lesion, and finally the significance of the 48 hour study. The ^{32}P test provides aid in differentiating malignant from benign ocular lesions and helps to reduce the percentage error in the diagnosis of ocular neoplasia.

POST-OPERATIVE COMPLICATIONS OF LEVATOR SURGERY. S. A. Fox, *Arch. Ophthal.*, March, 1961.

THE author believes that when levator action exists in ptosis, then any surgery other than strengthening of the levator is wrong. The most common complication is under-correction, which should not be diagnosed until all post-operative reaction has subsided. If the under-correction is gross, then a second operation can be performed. The commonest cause of under-correction is failure to resect sufficient levator. A poorly-developed or fibrotic levator may produce under-correction. Over-correction is less common, and is due to a too-liberal resection. If the over-correction is too great, then the levator should be recessed. Lagophthalmos may follow over-correction, or may be due to failure to separate the levator from its connexion with the supra-adjacent fascia orbitalis. Entropion, a poor lid fold, lid lag, notching of the lid and corneal involvement are other complications.

THE TREATMENT OF OCULAR TOXOPLASMOSIS WITH SPIRAMYCIN. J. B. Chodos and H. E. Chodos, *Arch. Ophthal.*, March, 1961.

THE authors report on the use of spiramycin in toxoplasmic uveitis. Sixty-seven patients with acute active chorio-retinal lesions of toxoplasmic origin were treated with spiramycin for approximately six weeks. Steroids were used also in 45 cases and withheld in 22 for control purposes, except in three in which there was a medical contra-indication. In the group treated with spiramycin and steroids, 40 patients or 88·8% were considered cured, whereas in the series given spiramycin only, 20 or 90·9% were cured. All patients gave a positive response to the Sabin-Feldman methylene-blue test with titres in dilutions of at least 1 in 16. Of the patients considered cured, three had a relapse within one year, and the relapse was easily controlled with spiramycin and steroids. The authors state that if vitreous haze resulting from the chorio-retinal lesion has progressed to a point at which the fundus is no longer visible, usually neither spiramycin nor steroids will result in clearing of the

vitreous. Prognosis depends largely on the state of the vitreous at the start of therapy, and so treatment should be commenced as soon as possible. As the result of the dye test is not available for several weeks, the authors used the toxoplasmin skin test as a diagnostic aid. Patients who give a positive result to the skin test, and who have a positive epidemiological history, active chorio-retinal lesions and no other ætiological factor, should be treated at once with spiramycin. The authors recommend 2 grammes of spiramycin daily in a single dose, treatment to continue for six weeks. In addition methylprednisolone was given in a dosage of 4 mg. three times a day followed by 4 mg. twice a day and then tapered, and continued so long as spiramycin was given. In addition, methylprednisolone was used locally together with mydriatics. Ascorbic acid was given in a dosage of 250 mg. per day, and it was thought that patients receiving vitamins did somewhat better in the clearing of the vitreous and cells.

HYPOPARATHYROIDISM, PSEUDOHYPOPARATHYROIDISM AND PSEUDO-PSEUDOHYPOPARATHYROIDISM. H. Hanno and D. Weiss, *Arch. Ophthal.*, February, 1961.

THE authors briefly review these three related disorders. In hypoparathyroidism, whether post-operative or idiopathic, cataract is the important ocular defect. The lens changes are bilateral and chiefly lamellar in type, and involve subcapsular areas of the cortical portion of the lens. Early treatment will prevent formation of lens opacities, but once formed they are irreversible. Papillœdema and increased intracranial pressure may also occur. In pseudohypoparathyroidism the average age of onset is eight years; the disease usually manifests itself by the age of 20. Females predominate in the ratio of 2:1. Lens opacities occur similar to those seen in hypoparathyroidism. In pseudo-pseudohypoparathyroidism there is no hypocalcæmia, but other features of pseudohypoparathyroidism are present. The ocular feature is the presence of blue scleræ.

TRANSIENT MYOPIA AND RETINAL EDEMA DURING HYDROCHLOROTHIAZIDE THERAPY. F. J. Beasley, *Arch. Ophthal.*, February, 1961.

THE author reports a case of transient myopia and perimacular œdema secondary to the use of 100 mg. of hydrochlorothiazide, a non-mercurial diuretic for oral use. The patient was a woman, aged 21 years, who was in the last few weeks of her first pregnancy. Her blood pressure was normal, but there was œdema of the lower extremities. Blurred vision occurred after she had taken 100 mg. of hydrochlorothiazide. The myopia cleared three days after cessation of the drug, and the perimacular œdema cleared after four days.

RETINAL DETACHMENT SURGERY. P. R. McDonald, *Amer. J. Ophthal.*, December, 1960.

THE author analyses the records of 100 patients operated upon for retinal detachment. Three patients aged under 10 years were boys, and there was a history of trauma. Two patients were aged over 80 years, and the detachment occurred in their only seeing eye, which was aphakic. Eight patients had direct trauma and three had a history of indirect trauma. Twenty-three patient had bilateral detachments. Sixteen patients had more than 3 dioptres of myopia, and 32 patients were aphakic. A total of 125 operations were performed on these 100 patients. The use of a scleroplastic flap with an encircling tube was the primary procedure in 64 patients. Of the 100 cases, 19 were listed as failures. Failures were due to poor visibility, large multiple tears, vitreous contraction, vitreous hæmorrhage and uveitis. Five cases were failures owing to faulty operative technique or judgement.

MACROGLOBULINEMIA AND ITS EFFECT ON THE EYE. J. T. Coyle *et alii, Arch. Ophthal.*, January, 1961.

THE authors state that macroglobulinæmia is the presence of abnormal amounts of an abnormally high molecular weight globulin in the plasma. It is a rare disease occurring primarily in males aged over 50 years. There is no typical ophthalmoscopic picture; the appearances may include punctate hæmorrhages, superficial linear hæmorrhages and bilateral venous branch thromboses. The abnormality is on the venous side, and it tends to progress; dilatation and tortuosity of the veins are present, and the disc and arterioles are relatively normal. The condition is to be differentiated from multiple myeloma, leukæmia and certain collagen diseases with associated secondary macroglobulinæmia. The prognosis is poor. Anti-leukæmic therapy has produced remissions in some cases, and more recently plasmaphoresis has been used. This consists of taking whole blood from the patient, centrifuging it, discarding the plasma and retransfusing the patient with his own packed cells.

ENZYMATIC ZONULOLYSIS IN LENS EXTRACTION. J. Barraquer, *Arch. Ophthal.*, January, 1961.

THE author reports on the use of enzymatic zonulolysis in 757 intracapsular lens extractions with particular reference to complications. With the use of zonulolysis there was a higher incidence of complications resulting from poor wound healing — namely, delayed reformation of the anterior chamber, anterior synechiæ with hypertension, reopening of the corneal wound, iris prolapse and late loss or flattening of the anterior chamber. A more frequent but less important complication is subconjunctival filtration. In an endeavour to prevent these complications, the author modified his original technique. He describes this technique in detail. He summarizes the important details as follows. The incision should be 1 mm. from the limbus in the scleral vascularized area with a conjunctival flap, suturing should be carefully done and the enzyme should remain in the eye the shortest possible time. Enzymatic zonulolysis makes lens extraction easier in the 30 to 60 years' age group, and it makes possible total extraction in the 20 to 30 years' age group. Even with the use of the enzyme, total extraction is still difficult in the 10 to 20 years' age group. Its use is contraindicated in children younger than 10 years.

LOCAL ADMINISTRATION OF ANTICHOLINESTERASE AGENTS IN OCULAR MYASTHENIA GRAVIS. I. H. Leopold *et alii, Arch. Ophthal.*, March, 1960.

THE authors briefly review the treatment of myasthenia gravis and then give their experiences with the effect of locally applied anticholinesterase agents in ocular myasthenia gravis. Their work indicates that locally administered neostigmine and demecarium bromide ("Humorsol") will bring about definite improvement in the function of extra-ocular musculature affected by myasthenia gravis. Ptosis appeared to be particularly relieved in five of seven patients. Diplopia was minimized in two patients. This approach appears to have potential as adjuvant therapy to the systemic administration of neostigmine. The programme for each patient must be worked out individually. There are disadvantages in the local use of these drugs—namely, ciliary spasm, miosis, headache and difficulties in accommodation.

THE STRUCTURE OF THE TRABECULAR MESHWORK IN RELATION TO THE PATHOGENESIS OF OPEN ANGLE GLAUCOMA. J. S. Speakman, *Canad. med. Ass. J.*, May 13, 1961.

THE author undertook a study in an endeavour to establish accurate criteria for the normal morphology of the trabecular meshwork, so that pathological changes which might be of significance in the pathogenesis of chronic simple glaucoma could be assessed with greater confidence. Using the eyes from premature and full-term babies and infant and adult eyes, the author studied the trabecular region by dissecting the meshwork in layers from the anterior chamber to Schlemm's canal, and teased fragments of whole fibres were examined as wet preparations. The study included an examination of the structure of the drainage channels, an examination to determine the presence and distribution of acid mucopolysaccharide which was found inside the trabecular fibres between the fibre bundles of collagen, and a study of the proliferative and degenerative changes in the trabecular meshwork.

MARCHESANI'S SYNDROME. J. Levy and P. E. Anderson, *Brit. J. Ophth.*, March, 1961.

THE authors state that Marchesani's syndrome is characterized by skeletal and ocular abnormalities. The stature is short, the figure is stocky and the skin and subcutaneous tissue are thick. The hands are spade-shaped with broad palms and short, stubby fingers. The ocular features are spherophakia and ectopia lentis giving rise to lenticular myopia and iridodonesis and glaucoma. The condition is generally familial, and in a high proportion of cases there is consanguinity of the parents. The treatment of the glaucoma is difficult. Miotics may produce a rise in tension. The authors describe a case in which the glaucoma in one eye was controlled by an ab-externo iridectomy performed before secondary changes appeared in the filtration angle.

Brush Up Your Medicine.

CANCER CHEMOTHERAPY.[1]

SOME FORMS of cancer chemotherapy can be carried out by a patient's own doctor as well as, and perhaps better than, by specialized hospital departments. Although surgery and radiotherapy, either singly or in combination, remain the two principal methods of treatment, chemotherapy either alone or in combination with the traditional approaches may provide further control of cancer. The requirements for good ambulatory care are modest. They are: (*a*) an interest in this form of therapy by the family doctor; (*b*) hæmatological and radiological facilities; (*c*) planning by surgeons, radiotherapist and physician at the commencement of treatment when a programme is tentatively decided. In this team, the family doctor can assume an important rôle.

It must be appreciated that only some 10% to 15% of patients will achieve useful regression and objective improvement and perhaps another 25% will obtain pain relief and satisfying palliation. The remainder will not be helped, and there is a not insignificant risk that some may be made worse. The choice of treatment is therefore not an easy one, even when the decision is shared by several doctors. No reliable method of predicting the effects of a chemical in any particular case exists as yet. All chemotherapeutic agents depress the bone marrow, and as a rule, the dose needed to cause regression significantly affects the marrow. Regular blood counts, measurement of the size of lesion and radiological changes should be carefully recorded. The few minutes needed in preparing a sheet of graph paper for recording blood counts, doses and responses are very well spent, compared with the accumulation of a heap of individual reports. Leucopenia (fewer than 4000 leucocytes per cubic millimetre) must be watched for, as must sore throat and bruising. When a fall in leucocyte count occurs, the patient has to be carefully and frequently supervised, as the depression is usually temporary and recovers spontaneously within several days. Fever and infection require appropriate antibiotics, nutrition must be maintained, and vitamins, especially vitamin B_{12} and folic acid, may help marrow regeneration. Steroids, hormones and iron are not needed.

Reticuloses and Leukæmias.

It is in these conditions that the general practitioner can play his most important rôle. Certain principles of treatment are well established and differ from those in carcinoma and sarcoma. As this group of neoplasms is essentially multifocal and systemic and must eventually recur, treatment is designed to induce a remission with the smallest dose of radiotherapy or chemotherapy, in anticipation of the need for further therapy in the unpredictable future.

Localized masses are best treated by radiotherapy and occasionally surgery, while multiple widespread small lesions require treatment with chemicals. Systemic disturbances, such as weight loss, fever and pain, indicate the need for systemic treatment, but the decision should be made by the team. Whether the dose is massive or low and intermittent will be dictated by the urgency of symptoms, and the dose may be altered by the response of the tumour.

Chronic lymphatic leukæmia, especially in the older age groups, is a relatively benign disease and may require little if any treatment. The total leucocyte count is of slight importance, and treatment is reserved for changes in hæmoglobin levels, enlarging glands or hæmolytic episodes. Nitrogen mustard given intravenously is needed for acute symptoms, but oral therapy is usual and may be given with T.E.M., "Nitromin", "Chlorambucil" or "Endoxan".

Chronic myeloid leukæmia dictates its treatment via leucocyte and hæmoglobin levels, and continuous suppressive therapy with "Myleran" is most commonly used.

Malignant Diseases in Childhood.

In general, the principles discussed above will apply, but some modification is often necessary because of the different behaviour of pædiatric malignant disease and the special need to protect the child and the family from unnecessary suffering. Traumatic investigations and procedures, unnecessary hospitalization and the use of therapeutic agents producing unpleasant or painful effects must all be avoided if possible. The following forms of malignant disease require special consideration.

Leukæmia.

This is the most common form of pædiatric malignant disease, and the disease which most concerns the general practitioner, who should play an important part in its management. To restrict these remarks to the most common form, acute leukæmia of lymphoblastic origin, it can be stated that this is a most acute malignant process which, if untreated, produces death within a few weeks of its clinical appearance. Present methods of therapy in most cases will modify the disease so that remissions lasting many months to several years may result. In these remissions the child is well and able to lead a normal life for most of the time. Treatment is carried out immediately after confirmation of the diagnosis and after a full explanation has been made to the parents. This explanation should include a discussion of the proposed plan of treatment, and if possible the general practitioner caring for the child should be present.

Initial Treatment.—This may or may not require the child's admission to hospital. Transfusion is given if necessary. The basis of the treatment is steroid therapy, and prednisolone is given in a dosage of 80 to 100 mg. per square metre per day until a remission is obtained. In favourable cases this occurs within three or four weeks, and if it has not occurred within six weeks a satisfactory remission is unlikely. In addition, 6-mercaptopurine may be given in a dosage of 2·5 mg. per kilogram per day.

Maintenance Therapy.—This, so far as possible, is carried out at home, with the child leading a normal life. Continuous small doses of prednisolone may be used; probably more satisfactory are alternating three-month courses of 6-mercaptopurine and "Methotrexate". The dose will vary with each case.

Relapses.—Full doses of steroids are given with or without 6-mercaptopurine and with transfusions if necessary. The patient's admission to hospital may or may not be required. Palliative deep X-ray therapy may be necessary to relieve the signs of central nervous system involvement if they occur, and it is justified for those patients who are otherwise having a satisfactory remission. Further attempts to prolong life should be avoided when an obvious terminal stage is reached.

Wilms' Tumour.

This is a potentially curable type of malignant disease if the diagnosis is made and treatment is carried out before renal vein invasion occurs. Diagnosis should be established with minimal delay and with minimal handling on examination. A satisfactory system of treatment is as follows: Day 1, "Actinomycin D", 75 to 100 μg per kilogram per day in three or four divided doses; Day 2, radical nephrectomy; Day 3, commencement of radiotherapy to the paraaortic and mediastinal nodes. If metastases have occurred, some palliative chemotherapy and surgical removal may be considered.

Neuroblastoma.

Because of the occasional known spontaneous disappearances of this tumour in children aged under two

[1] This article was prepared by request after consultation with the Medical Director of the N.S.W. State Cancer Council. It is supplementary to the comprehensive survey by Kenneth R. Cox published in the issues of October 14 and 21, 1961.

years, in this age group attempts to prolong life with chemotherapy seem justified. "Endoxan" may be given by mouth, or at intervals in large doses of 50 mg. per kilogram with limb exclusion. It should be pointed out that chemotherapy of this type often controls pain more satisfactorily than any other method.

Carcinoma and Sarcoma.

The indications for chemotherapy in these lesions are not as clear-cut as they are in the leukæmias and reticuloses, and chemotherapy should be exhibited only to those patients who have been ruled unsuitable for surgery or radiotherapy. It is always advisable that the decision as to unsuitability for conventional forms of therapy be made by appropriate clinics and that the decision as to the method of chemotherapy be decided at the centre. Bulky tumours should whenever possible be excised before chemotherapy commences. Some patients will be recommended for ambulatory therapy on prolonged small dosage of the chosen drug, while others will be recommended for intermittent large dosage, and it is in the management of these two groups that the local practitioner can play an active part.

On some occasions patients will be recommended for massive doses of drugs, protection being conferred on the patient by using marrow-sparing techniques, and on yet others isolated limb perfusion will be employed with large doses of the drug and a pump oxygenator. These methods are available only in the large centres, but the family doctor will be called upon to assist with the patient's after-care. It is suggested that practitioners keep careful records of the patients treated by chemotherapy. The New South Wales State Cancer Council is hopeful that it may soon be able to establish a cancer chemotherapy registry, for which a simple punch-card record can naturally help in assessing the value of various forms of therapy.

Conclusion.

Team-work is the keynote to good management of the cancer patient, and even with the most elaborate and specialized methods it remains an art which develops with experience and interest. Enthusiasm, understanding and care should never be overshadowed by cold science. Cancer chemotherapy is slowly becoming established as a form of treatment. With care it becomes increasingly valuable, but used unwisely it will cause harm. It should be used to help the living and not to try to revive the dying.

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British Medical Association.

NEW SOUTH WALES BRANCH: SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on June 29, 1961, at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney, DR. E. S. STUCKEY, the President, in the chair.

The Time Factor in Surgery.

DR. E. WILSON read a paper entitled "The Time Factor in Surgery" (see page 699, issue of October 28, 1961).

DR. G. C. FISK read a paper entitled "The Time Factor in Surgery" (see page 703, issue of October 28, 1961).

DR. T. F. ROSE, in opening the discussion, said that looking at Dr. Wilson's diagrams, and considering his talk on parabolic curves, and Dr. Fisk's comments on geometrical and arithmetical progression one realized why the University of New South Wales now had mathematics in the early part of its medical course. Dr. Rose said that he was also at one with Dr. Wilson when he did not call a physician into consultation prior to operation. It was well known that modern anæsthetists were trained physicians. If the surgeon called in an ordinary physician, it seemed that he was being asked to examine a patient to see whether he was fit for an operation he had probably never seen to be performed under an anæsthetic of which he had never heard. The anæsthetist should be asked to state whether he considered the patient fit for operation. Dr. Rose then said he proposed to discuss the time factor before operation. Dr. Wilson had not mentioned one of the greatest advances in surgery—air-conditioning of the operating theatre; it had to a great extent abolished the element of fatigue. That was particularly brought to mind in recent heat-wave conditions when the air-conditioning broke down in some theatres; one realized what the older surgeons had to suffer. The surgeon now had to a great extent given up fatigue as an excuse for his failures, and air-conditioning was also very good for the patient. Dr. Rose said that in many diseases the time factor before operation was most important. Referring to cancer, Dr. Rose said that although the statisticians told the surgeons that whatever they did, they could do no good and would probably do harm, nevertheless the surgeon and the patient did not feel the same way. That was why a patient with cancer should be operated on as soon as possible. The time factor in those circumstances was important, not only from the surgeon's point of view, but also from the patient's peace of mind. There was no use in having cancer diagnostic clinics if the person who was to have an examination was given an appointment for some months ahead. Patients with suspected breast cancer, for example, should be operated on the day after the provisional diagnosis had been made if possible (naturally, after adequate preparation), in order to see whether they had cancer or not. Dr. Rose mentioned a patient who had four years previously been suspected of bowel cancer which had not been investigated; he had operated on her on the day of the meeting when she had intestinal obstruction from it. She was found to have an inoperable cancer of the colon. The time factor was also important in the more acute surgery. Patients with acute inflammation should be operated on as soon as possible. If acute appendicitis was treated in the early stages of the disease, there should be no mortality and very little morbidity. If the surgeon for some reason decided to give the patient antibiotics and defer operation, the disease might spread beyond the appendix and the operation might become one with some mortality and a good deal of morbidity. The time factor there was most important, as it was in the case of acute intestinal obstruction, in which the surgeon wished to operate as soon as he could; there might be a piece of strangulated bowel to be freed. However, the anæsthetist might insist that the patient's electrolyte balance should be put right. The result was a race between the electrolyte balance and the bowel rapidly losing its blood supply. Again, in internal hæmorrhage, the surgeon might have to operate in a hurry; the anæsthetist helped with blood transfusions before and during operation, to allow of the least possible delay. Dr. Rose then referred to the time factor in the post-operative period. He pointed out that the surgeon must be able to recognize straight away acute dilatation of the stomach, or he would lose his patient very quickly. If the condition was treated immediately, then the patient's life would be saved. Acute pulmonary collapse had to be recognized very quickly. Also, of course, during operation the recognition of cardiac arrest was most important. The time factor there was a matter of three minutes at the most, and the surgeon had to be prepared to perform cardiac massage straight away no matter what his specialty was.

DR. M. C. MCKINNON asked Dr. Wilson what he regarded as the best position for the patient in gall-bladder operations, and whether he used the gall-bladder block or some other method of obtaining a good exposure. Dr. McKinnon said that in Wollongong they had for some time been using what they referred to as the South African position, because it was described by a South African surgeon whose name he had forgotten. A sandbag about the size of a small plum pudding was placed under the buttock on the right side, and the patient's shoulders were allowed to sag back on the table and his right hand was drawn up under his left

ear. The surgeon stood on the left side of the patient. Dr. McKinnon asked for Dr. Wilson's opinion on that position, and also what position he used for cholecystectomy.

Dr. Wilson, in reply, said that he did not use that position. Although Dr. McKinnon's suggestion had much to recommend it, he, himself, if he tried operating on the left side of a patient for a cholecystectomy, felt back to front. To him it was rather like carrying out a rectal examination with the patient on the right side; it seemed to be the wrong way round. Perhaps that impression was due to habit. On the other hand, if there were many adhesions to be divided, he went round to the left side for a while, and when they were freed he went back to the right. Ideally, surgeons should be ambidextrous, and then it would be just as easy to operate from either side. Referring to the question of exposure, Dr. Wilson said that he almost always used a transverse incision, and no block or sandbag. It he was having difficulty, he asked the anæsthetist for more help.

DR. S. V. MARSHALL said that after a somewhat prolonged experience he preferred the slow surgeon to the rapid and slap-dash type, who seemed to think that it was possible to knock a patient flat with an anæsthetic, and to drain him of blood and put it back with impunity. Dr. Marshall preferred the man who would take his time to do the job, though he disliked the surgeon who took six to eight hours to perform an operation, exhausting himself, the anæsthetist and the patient as well. He liked the happy-medium man, who did a good job, taking reasonable care, and did not expect too much of the anæsthetist's abilities.

DR. C. SARA said that he had enjoyed both papers, and that Dr. Wilson's paper had been friendly to the anæsthetist, since he advocated surgery that was not too fast and not too slow. As Dr. Wilson had said, the first part of his paper was purely statistical. The second part was intensely practical, and it was to be hoped that some of the surgeons would try to introduce some of the time-saving factors advocated by Dr. Wilson. Dr. Sara said that he could confirm the story of the surgeon related by Dr. Wilson, since he himself had been his anæsthetist for a short time during his resident days. The surgeon used to perform an appendicectomy while the patient was still under ethyl chloride. The anæsthetist was directed to fill the bottle of ether and spray on the ethyl chloride. By the time the anæsthetist turned round to pick up the ether, the surgeon was on the way out. Dr. Sara said that he had done that surgeon's work for some months, and there was no mortality and as far as he could remember no morbidity. That surgeon was also one of the first advocates of early ambulation. Not only was the patient in the operating theatre for a short time, but he was in bed for a very short time. Dr. Sara went on to say that he had been interested in Dr. Fisk's short paper. He had understood Dr. Fisk to say that there were no physiological reasons for not having a long operation. Swann did not agree with him about the effects of anæsthetics on the cortico-steroids. As he had said, thiopentone and spinal anæsthesia protected both parts of the adrenals; but if the anæsthetic was prolonged, whether an operation was performed or not, there was an intense output of cortico-steroids and both parts of the adrenal became exhausted. The only other protective device in that regard was hypothermia. Dr. Fisk had said that there was a temporary effect of pulmonary ventilation. Dr. Sara said that he did not quite believe that either; but of course the longer the anæsthesia proceeded, the more desaturated the hæmoglobin became, and it was not all the anæsthetist's fault. That also occurred and was more intense with thoracic procedures; again, it was not entirely the anæsthetist's fault. Dr. Sara went on to say that one other point he had thought of was the cause of fatigue occurring in both surgeons and anæsthetists. The psychologists called it "fascination" (not fascination of the anæsthetist for the surgeon or of the surgeon for the anæsthetist). All anæsthetists could name the surgeons who could not see the wood for the trees. Thy might have the same piece of bowel in their hand for an hour and a half, and nothing happened. The same thing could happen with the anæsthetist; he got hold of a bag, put his head on the pillow and became fascinated with the bag, forgetting about the over-all problems of resuscitation. However, life was a matter of chance, and most procedures in medicine carried with them calculated risks. The longer an anæsthetic procedure persisted, and the longer the surgery went on, the greater the chance that some untoward incident might occur.

DR. P. D. BLAXLAND said that, despite the continued desaturation of the hæmoglobin and so on, anæsthetics alone were probably not particularly damaging provided that they were skilfully given. He understood that, because of the complications of tetanus, some tetanus patients were sometimes held under relaxants with some form of anæsthetic agent for very long periods. He thought that that probably showed that anæsthetics alone were not damaging.

Dr. Sara said that when tetanus patients were held under curare with hyperventilation, no narcotic or analgesic drugs were usually given. When those same patients were held under nitrous oxide anæsthesia, some developed rapidly advancing hypoplastic anæmia and some proceeded to adrenal exhaustion.

Dr. Blaxland said that it seemed possible to hold patients under analgesics for a very long time without complications except their bronchial secretions. He wondered whether in the long procedures anæsthetists found it necessary or desirable to perform bronchoscopy at some time during the anæsthetic. The other point was the question of water loss. He was sure that the water loss of the patient was great; often the surgeon found himself dehydrated at the end of the operation.

Dr. Sara said that the over-all recovery rate in the patients mentioned by Dr. Blaxland varied from 36% to 46%. Most tetanus patients still died.

DR. D. G. FAILES said that he agreed with most of the statements that had been made. He thought that all would agree that the most important thing was that surgical procedures should be carried out as efficiently and skilfully as possible. The speed should be merely a by-product of the procedure. When the procedure was very extensive and would necessarily take a long time, he thought that there was much to be said for the suggestion of having two operative teams. Fatigue was certainly a factor in such procedures. Dr. Failes thought that it occurred much earlier than in Dr. Wilson's suggested four or five hours. Recently a Melbourne surgeon, who had made a particular study of the question of fatigue, had been in Sydney. He said that where he was working they found that about an hour and a half was as long as they could work at top pitch, and the change-over was made, not when it was suggested by the operating surgeon, but when the person who was to take over, and who was watching, thought it was time. They found that the method worked well. The average operating time they found was about an hour and a half. Dr. Failes said that Dr. Wilson had not mentioned the use of tourniquets, to stop bleeding and therefore perhaps to save time. He asked his views on the question.

Dr. Wilson, in reply to Dr. Rose, said that he had apparently been implying that he (Dr. Wilson) operated like a mathematician—in other words, with attention to detail. In reply to Dr. Failes, Dr. Wilson said that he agreed that one could become tired in less than four hours; he certainly did. He knew nothing about the Melbourne surgeon referred to. As far as the tourniquet was concerned, he had rather strong views on it; he disliked it. In his opinion one of the causes of infection was the use of tourniquets and bandaging the wounds after suturing them without obtaining hæmostasis. Under these circumstances the orthopædic surgeons especially were inclined to blame the dust in the atmosphere or someone's sinuses rather than the hæmatoma for the resulting infection. Dr. Wilson said that he thought that if a tourniquet was not used to get hæmostasis, the body, as it did on other occasions, dealt with the odd infecting organisms that entered from various sources (sweat glands and so on). It was one of the tenets of surgery not to leave hæmatomas behind.

Dr. Fisk, in reply to Dr. Sara, said that he had actually said that any surgical operation involved a physiological as well as an anatomical assault, and that that increased with the duration of the operation. However, he had suggested that the increase was not proportionate as time went on, and the statement that was being challenged apparently was that from the physiological point of view in a healthy, well-prepared patient, the time factor was not the most important factor in planning the operation. He thought the question of cortico-steroids was very controversial; but he agreed that the question of adrenal exhaustion would be important, although intricate. He had said that hyperventilation was a temporary arrangement. He thought it possible that there was more than one person who had indulged in hyperventilation or been passively hyperventilated at some time in their lives, and it was to be hoped that they had recovered from the effects by that time. In the respiratory unit at the Churchill Hospital, Oxford, they had patients whom they treated with intermittent positive pressure respiration for a number of diseases. They were a specialized unit, and they had reduced the technique to a fairly fine art. They had a similar high mortality with tetanus; but, on the other hand, they had

patients with poliomyelitis who had been hyperventilated for many days or weeks with a very low mortality, in view of the pulmonary problems involved. However, the research officer in charge of the unit had told him that most of their patients, to be kept comfortable when conscious, were ventilated to a pCO_2 of about 20, or between 20 and 30. They were all alkalotic, and in the long run there were no ill effects. They were still studying the subject. Dr. Blaxland had commented on bronchoscopy. Dr. Fisk thought that bronchoscopy during operation might be rather unpopular with the surgeons, unless they could send them out for tea; but he felt strongly that when secretions of any amount and of any viscosity were concerned, it was a simple matter to remove them with the bronchoscope. It was less traumatic than the blind insertion of a catheter through an endotracheal tube, and if proper precautions were taken, less traumatic to the patient and less likely to produce anoxia. The essential thing was that secretions must be removed efficiently and from all areas. Dr. Fisk thanked Dr. Marshall for his statement, with which he entirely agreed. Commenting on gall-bladder operations, Dr. Fisk said that he had strong views on them. He considered that, even when no rests or unnatural positions were employed, retraction itself in an attempt to expose structures near the posterior abdominal wall could have the most deleterious effect, probably owing to interference with venous return from the lower half of the body. He believed that Dr. Davidson had some results which showed how that occurred. Certainly he believed that many patients deteriorated rapidly while the gall-bladder bed was being exposed, and underwent a remarkable recovery as soon as the hand or retractor or packing was removed from the abdomen. Dr. Fisk finally thanked Dr. Rose for his remarks, and expressed regret that he confined himself to one of the time factors in surgery; he acknowledged that the other time factors were important too. Particualrly was that so in that speed was of the essence in cardiac arrest and in other disasters that tended to arise from time to time.

Dr. Stuckey, from the chair, said that all were agreed that both anæsthetists and surgeons' activities were more likely to harm the patient the longer the operation lasted, and that therefore speed was desirable provided certain basic essentials of safety were not sacrified. In particular, they should ensure the best possible condition of the patient prior to the operation, quiet movements, gentle handling of tissues with hands, retractors and instruments, diligent hæmostasis, patient dissection where vital structures could be harmed, meticulous coaptation of tissues, especially when that applied to anastomosis, and the efficiency that came from adequate training.

Out of the Past.

PHARMACISTS AND THE MEDICAL PROFESSION.[1]

[From the *Australasian Medical Gazette*, August 20, 1904.]

AN important circular which bears out the truth of recent statements in our columns, has been drawn up and signed by all the principal dispensing chemists in Sydney and suburbs, and forwarded to all members of the medical profession in the district. The circular is as follows:

Gentlemen, — A matter of supreme moment, not only to us as practising pharmacists, but having an even more pressing importance to members of your profession, impels us to address you. We wish to call your attention particularly to the prescribing of *patent and proprietary medicines*, and especially to medicines packed in tablet forms. There is a growing tendency nowadays to economise time; the quickest, easiest way seems always to be selected. This, we think, is one reason physicians so frequently prescribe drugs in tablet form, and mixtures of proprietary origin. The ultimate effect of this is that self-medication among the general public has reached astounding proportions. It is now an everyday experience to be called upon by the public to supply not only such "simples" as bicarbonate of soda, cascara, etc., but such potent and dangerous drugs as chloralamide, erythrol, Easton's syrup, etc., in tablet form. Almost daily do we find instances of patients receiving a prescription ordering some readily decipherable tablet remedy, and, in place of presenting the prescription, merely asking for X.Y.Z.'s tablets of the drug ordered, and then disclosing the prescription in order to get the directions. From this it is an easy step to the almost invariable result of the patient recommending the remedy prescribed for himself to his friends without the intervention of the physician . . . *Cui bono*? The physician benefits not at all, the pharmacist but little more, the consumer very possibly is injured by improper treatment—the manufacturer extends his premises and floods the physician with fresh literature and samples. Briefly, the position resolves itself into—a financial loss to the physician, and a danger to the public.

[1] From the original in the Mitchell Library, Sydney.

Medical Matters in Parliament.

HOUSE OF REPRESENTATIVES.

THE following extracts from *Hansard* relate to the proceedings of the House of Representatives.

October 17, 1961.

Hospitals.

MR. SWARTZ asked the Minister for Health, upon notice—

1. Was the new thoracic block and Commonwealth Health Laboratory at the General Hospital in Toowoomba financed by a Commonwealth grant and is the operation of this special hospital subsidized by the Commonwealth?

2. What was the total cost of the building with all equipment?

DR. DONALD CAMERON: The answers to the honourable member's questions are as follows:

1. Yes.

2. The amount reimbursed by the Commonwealth Government to the Queensland Government in respect of the capital cost of the thoracic block was £283,085.

October 19, 1961.

Dental Treatment.

MR. THOMPSON: I ask the Minister for Health whether consideration has been given to extending the provisions of the medical benefits legislation to cover dental treatment. It has been brought to my notice that many dentists in South Australia are complaining that their business has fallen away to a considerable extent because people are unable to pay for necessary dental treatment. As sound health is as dependent on good teeth as on other factors, I ask the honourable gentleman whether anything is being done to have the medical benefits scheme extended to cover dental treatment.

DR. DONALD CAMERON: A good deal of consideration has been given from time to time to the question raised by the honourable member. Of course, it would be wrong to suppose that an insurance scheme should be devised so that benefits will be in line with fees charged by independent professional practitioners; and there are great difficulties associated with establishing a system of voluntary insurance to cover dental benefits. In Australia, we have a system of voluntary insurance, but it is quite different from a system of compulsory insurance and involves quite different considerations. If dentists are experiencing difficulty because of the height of their fees, I must suggest to the honourable member that there is a very obvious remedy.

October 24, 1961.

Medical Benefits.

MR. L. R. JOHNSON asked the Minister for Health, upon notice:

1. Is it a fact that some medical benefits funds do not give rebates for refractions by registered optometrists as well as those by ophthalmologists?

2. Do the Medical Benefits Fund of Australia and the Hospital Benefits Fund of Victoria discriminate against optometrists by limiting payment of supplementary benefits to patients who have been referred to an ophthalmologist by a general practitioner?

3. Is any Commonwealth benefit payable for optical treatment?

4. Is it a fact that, as the Medical Benefits and the Hospital Benefits Fund now stands, in order to claim a benefit the patient has to go from the optometrist to the

ophthalmologist, to the general practitioner, to get a "referral", then back from the general practitioner to the ophthalmologist and, finally, in many cases, to a particular dispensing shop, if the ophthalmologist prescribes glasses?

5. Has the Government been asked by the Australian Optometrical Association to amend the *National Health Act* so as to require medical benefits funds to give rebates for refractions carried out by optometrists as well as those carried out by other registered practitioners; if so, what decision has the Government made in relation to this request?

6. Has the Government given consideration to inserting in the *National Health Act* provisions for optometrical services which will include the payment of Commonwealth benefits similar to those paid in respect of hospital and medical benefits; if so, is any action contemplated in this matter?

DR. DONALD CAMERON: The answers to the honourable member's questions are as follows:

1. Yes.

2. No. The funds also pay a fund benefit where a patient consults an ophthalmologist without being referred by a medical practitioner, but a higher fund benefit is payable where the patient is referred to the ophthalmologist by a medical practitioner.

3. Commonwealth benefits are payable for a wide range of ophthalmological services by medical practitioners.

4. No.

5. and 6. The Government has considered such representations from the Australian Optometrical Association but no amendment of the *National Health Act* in this regard is contemplated at present.

October 26 and 27, 1961.

Antibiotics.

MR. WHITLAM asked the Prime Minister, upon notice:

1. Has Professor F. P. Dwyer of the Australian National University discovered an antibiotic which is unusually effective in the treatment of staphylococcal and other highly resistant infections?

2. Has the Australian National University arranged with a drug company to develop and test the discovery?

3. What is the name of this company?

4. What are the terms of the arrangement?

5. Did the university give the Commonwealth Serum Laboratories the opportunity to develop and test the antibiotic?

MR. MENZIES: The answers to the honourable member's questions are as follows:

1. to 5. I understand that following several years of research work conducted by Professor Dwyer in collaboration with associates in the University of Melbourne, a potentially useful series of biologically active compounds have been discovered. These have shown promise in the treatment mentioned in the question. However, this is a highly technical subject, and the manner in which these compounds may best be developed and tested is clearly a matter for decision by the governing bodies of the universities concerned. I suggest the most satisfactory course is for the Deputy Leader of the Opposition to direct his inquiry to the Australian National University itself.

SENATE.

THE following extracts from *Hansard* relate to the proceedings of the Senate.

October 24, 1961.

Quarantine Regulations.

SENATOR MARRIOTT: My question is directed to my colleague, the Minister for Customs and Excise. Through you, Mr. President, I should like to take the opportunity to congratulate him on the fifth anniversary of his elevation to Cabinet rank. My question is: Has the Minister read the comments in the Sydney press by the chairman of Air India in which he referred to his mental anguish at filling in a passenger's baggage declaration on his recent visit to Australia. Can the Minister inform the Senate of the significance of the terms in the form mentioned by Mr. Tata?

SENATOR HENTY: I did read the comments of the chairman of Air India. I thought they were idle comments for a man in his position to make. It is easy enough to be facetious about regulations in any country. No doubt many of us could be just as facetious about regulations in any country. I shall discuss briefly the items on the Passenger's Baggage Declaration to which Mr. Tata referred because I consider they are of great significance. They deal with quarantine regulations in this country and as such they are most important. One item is, "Saddles, bridles, horse rugs or horse brushes", and another "Animals or animal products (including meats, salami, sausage, cheese, skins)", and things of that type which can carry germs and diseases from overseas that we do not have at this stage within Australia.

SENATOR HENDRICKSON: He never mentioned any of those things.

SENATOR HENTY: I do not know whether it is foot or mouth disease the honourable senator has. I think it is mouth disease. These regulations were inserted by the Department of Health, and they are designed—as the Government would wish them to be designed, and will see that they remain so designed—to keep from this country many of the dreadful diseases that exist in humans, animals and plant life in other countries of the world—diseases from which we are free in Australia.

Mr. Tata referred very facetiously to germ cultures, microbes, viruses, vaccines and bacterial cultures. Those are things which professors, who come here to lecture, or who come out here for the purpose of showing their experiments, regularly bring with them in flasks, and the Department of Health must have full information about them when they are entering into Australia. It is not a thing to worry any ordinary visitor who is not carrying germ cultures with him. I should have thought that a man in Mr. Tata's position would have recognized that fact.

SENATOR HENDRICKSON: He never mentioned that.

SENATOR HENTY: I think I heard coming from the Mouth again an interjection to the effect that Mr. Tata never mentioned that matter. I am talking about the press report of his statement and what he said to me last night.

SENATOR HENDRICKSON: What was that?

SENATOR HENTY: He said to me last night that he mentioned it and that is why I thought it was a rather facetious comment. I should like the Senate to know that the Government will continue to see that this part of the Passenger's Baggage Declaration is filled in and that the requirements are carried out to the full to ensure that none of the diseases which ravage other countries shall come into Australia if it is possible for our quarantine regulations to prevent them.

Australian Medical Congress.

FIRST SESSION, ADELAIDE, MAY, 1962.

THE following information has been supplied by the Executive Committee of the First Session of the Australian Medical Congress, which is to be held in Adelaide from May 19 to 26, 1962.

Provisional Programme.

The provisional programme is as follows:

Saturday, May 19: Registration. Sporting and social arrangements.

Sunday, May 20: Church services. Christian Medical Fellowship meeting. Private entertainment.

Monday, May 21: Registration. Opening of Pharmaceutical and Scientific Instruments Exhibition. Scientific Exhibition. Hobbies Exhibition. Private entertainment. Inaugural Ceremony. Opening of Congress. Presidential reception.

Tuesday, May 22: Scientific sessions. President's dinner and private entertainment.

Wednesday, May 23: Scientific sessions. Golf competition. Congress dinner.

Thursday, May 24: Scientific sessions. Garden Party at Government House. Henry Simpson Newland Oration.

Friday, May 25: Scientific sessions. Congress Ball.

Saturday, May 26: Excursions. Sporting fixtures.

Office-Bearers of Sections.

The Presidents and Honorary Secretaries of the various sections are, respectively, as follows:

Anæsthesia: Dr. R. A. Lewis (Tasmania); Dr. E. C. Hallett, 104 Brougham Place, North Adelaide.

Dermatology: Dr. E. Rosanove (Victoria); Dr. G. F. Donald, 163 North Terrace, Adelaide.

History of Medicine: Dr. J. E. Hughes (South Australia); Dr. P. F. Stratmann, 110 Kensington Road, Toorak Gardens, S.A.

Medicine: Sir William Morrow (New South Wales); Dr. H. Lander, Department of Medicine, University of Adelaide.

Naval, Military and Air Force Medicine and Surgery: Major-General A. J. Clyne (Victoria); Dr. J. D. Lister, 9 Raldon Grove, Myrtlebank, S.A.

Neurology, Psychiatry and Neuro-Surgery: Dr. K. B. Noad (New South Wales); Dr. R. H. C. Rischbieth, 254 North Terrace, Adelaide.

Obstetrics and Gynæcology: Dr. R. H. Macdonald (New South Wales); Dr. R. M. C. G. Beard, 188 North Terrace, Adelaide.

Ophthalmology: Dr. T. a'B. Travers (Victoria); Dr. D. O. Tonkin, 163 North Terrace, Adelaide.

Orthopædics: Dr. B. T. Keon-Cohen (Victoria); Dr. B. L. Cornish, 301 North Terrace, Adelaide.

Oto-Rhino-Laryngology: Dr. A. F. Quayle (Queensland); Dr. R. E. Gristwood, 172 North Terrace, Adelaide.

Child Health: Dr. Felix Arden (Queensland); Dr. H. M. Douglas, 80 Brougham Place, North Adelaide.

Pathology, Bacteriology, Bio-Chemistry and Forensic Medicine: Dr. A. V. Jackson (Victoria); Dr. P. R. Hodge, Department of Pathology, University of Adelaide.

Public Health, Industrial Medicine and Hospital Administration: Dr. P. S. Woodruff (South Australia); Dr. C. O. Fuller, Department of Public Health, 169 Rundle Street, Adelaide.

Radiology and Radiotherapy: Dr. B. S. Hanson (South Australia); Dr. L. V. Perrett, 170 North Terrace, Adelaide.

Rehabilitation and Physical Medicine: Dr. L. T. Wedlick (Victoria); Dr. A. W. Burnell, 178 North Terrace, Adelaide.

Surgery: Dr. I. B. Jose (South Australia); Dr. C. G. Wilson, 163 North Terrace, Adelaide.

Photographic Exhibition.

Medical practitioners who are keen photographers are invited to contribute to a photographic exhibition. Further information on this will be published in a special supplement in the issue of December 23. This will allow attention to be given to it during the holiday period.

Registration.

The Executive Committee stresses the importance of urgent application for registration. This is because of the difficulty in holding block hotel bookings after January 31, 1962. Application forms for registration are available from local State secretaries, a list of whom was published in the issue of November 25, 1961, at page 888, or from the Honorary Secretary, Australian Medical Congress, 80 Brougham Place, North Adelaide, South Australia. The subscription is £8 8s. plus exchange.

Inaugural Meeting of the Australian Medical Association

Intending members of Congress are reminded that the Inaugural Meeting of the Australian Medical Association will be held in Adelaide immediately before Congress—that is, on the evening of Saturday, May 19, 1962.

Correspondence.

THE PSYCHOLOGICAL CARE OF THE CHILD IN HOSPITAL.

SIR: On first reading the review of "The Psychological Care of the Child in Hospital" by Agatha H. Bowley, which appeared in THE MEDICAL JOURNAL OF AUSTRALIA on November 11, 1961, I was momentarily uncertain whether I was reading the book reviews or the correspondence section until the last paragraph, when the subject matter of the book was given passing consideration by your reviewer.

Presumably, amongst those pædiatricians who have been "carried away by the special needs of children", your reviewer includes the Committee of the Australian Pædiatric Association, whose report on children in hospital appeared in this journal on November 19 last year. It should not require more than the average attention span to appreciate that the Committee's terms of reference and recommendations were confined to the care of children who required admission to hospital because of the nature or severity of their illnesses, and that the scope of the report ranged a little beyond inner suburbia. The report specifically mentioned the care of children in remote areas and in small country hospitals.

It is encouraging for a teacher of children's medicine to read that there are some general physicians who recognize that "disease is disease no matter what the size of the body". The recent successful Plenary Session held by The Royal Australasian College of Physicians and the Australian Pædiatric Association in Adelaide last month would indicate that this attitude need no longer be considered daring. However, the main theme of the Australian Pædiatric Association's report was based on the precepts of Spence rather than Osler: that a person is a person no matter what the size of the body.

Yours, etc.,

Department of Child Health, W. B. MACDONALD.
University of Western Australia,
Perth.
November 20, 1961.

THE CONCENTRATION OF ADRENALINE IN LIGNOCAINE SOLUTIONS.

SIR: It is with caution that I approach the above subject. Anæsthetists nowadays are such erudite gentlemen that, however practical they may also be, they, should I dare argue with them, are able to retaliate so forcefully that I have little option but to retire to lick my wounds in the kennel where, by then, they make me feel I belong. I will, however, protect myself by confining my first remarks to facts as much as possible.

Dr. Holland and Dr. Blaxland complain that "Xylocaine" sold with 1 in 80,000 adrenaline is so dangerous that it "should no longer be sold to hospitals and doctors". They recommend all practitioners to insist that adrenaline concentrations never exceed 1 in 250,000. Unfortunately, most of us surgeons are out of date enough to think of such solutions in terms of minims of 1 in 1000 adrenaline solution per ounce, and to follow the more modern trend of terminology we have to do a little arithmetic. I make 1 in 80,000 of adrenaline approximately 6 min. of 1 in 1000 adrenaline per ounce, and 1 in 250,000 approximately only 2 min. per ounce.

In Newcastle, my erstwhile partners and myself removed thousands of tonsils using 7 min. of 1 in 1000 adrenaline to the ounce of 2% "Novocain". I never had one moment's anxiety from the anæsthetic, and, as far as I know, neither did they. If a death had occurred, I would certainly have heard of it.

I consider that 2 min. of 1 in 1000 adrenaline per ounce might prolong an anæsthetic, but is perfectly useless for hæmostasis. I have, therefore, never used less than 5 min. per ounce, usually 7 to 10 min. Saline solution containing this strength of adrenaline has been used by me frequently for diminishing oozing during anæsthetics (excluding chloroform or "Fluothane"), and again I have experienced no difficulties.

In certain operations blood can obscure the field, and especially serious interference with results be obtained. As an example, in cosmetic rhinoplasty, where great finesse is required to obtain a perfect result, injecting saline containing 10 min. of 1 in 1000 adrenaline to the ounce helps greatly.

When the fenestration operation arrived, it was discovered that the entry of blood into the bony external semicircular canal was a major catastrophe greatly diminishing the chances of recovery of hearing. I, therefore, followed Garnet Passe and routinely injected saline containing 20 min. of 1 in 1000 adrenaline to the ounce under general anæsthesia. I had no trouble, and I am sure as a result there are patients hearing today who would otherwise still be deaf.

With stapedectomy excessive bleeding is a major nuisance, and entry of the blood to the vestibule is deleterious without being quite the major catastrophe referred to in connexion with fenestration. Here I use the same solution of adrenaline in "Xylocaine" so strongly condemned by Dr. Holland and Dr. Blaxland, and again I have had no trouble. In America, stapedectomy clinics have to be seen to be believed. Patients are operated upon up to 12 in a day by a single surgeon. Teams of surgeons repeating the same operation day after day would soon find out if their regular routine was dangerous, and something would be done about it, particularly if the operation were not a life-saving one, and only done, as in this case, for deafness. Yet they inject high concentrations of adrenaline. Shambaugh, one of the giants in this field, at the Paris International Congress of Oto-Rhino-Laryngology this year, stated he used 2% "Xylocaine" containing adrenaline equal to approximately 80 min. to the ounce, but he only uses 1 ml. of total solution.

Naturally, I take certain precautions. Patients are never injected or operated upon sitting or standing up. Five minims of 1 in 1000 adrenaline to the ounce is not exceeded for children below the age of five years. Cases always have premedication. Before operating, I decide the maximum amount of solution I will use. This amount is measured and seldom all injected. For instance, for tonsillectomy 2 oz. is put out, but usually 1 to 1·5 is used. For fenestration, only half an ounce. For cosmetic rhinoplasty, 0·5 oz. of 20 min. solution, or 1 oz. of 10 min. solution. For stapedectomy, 3 ml., usually 2 ml. used. For extensive operations, as laryngectomy, etc., 3 oz. of 7 min. solution, only part being used at a time. The most important precaution I take is to inject slowly, and to observe all the rules which enable one to be sure none of the solution is ever injected intravenously.

Now I am about to "stick out my neck" and get on to theory. I believe there is more risk in a large amount of adrenaline being used in a weak solution than a similar amount in a more concentrated solution. If injected slowly, the more concentrated solutions cause quick vasoconstriction and reduction of rate of absorption. The main danger is, of course, direct injection into the blood-stream.

Starling stated years ago that "when adrenalin is injected into the bloodstream the effect is only temporary. It is not excreted in the urine, but rapidly disappears from the blood. It is easily oxidized and is extremely unstable in alkaline solution". Professor Cathcart taught that the life of adrenaline in the blood-stream was six seconds, but I know this time is long enough to upset the heart rhythm, though to do so very rapid absorption is necessary.

I have purposely avoided discussing the use of adrenaline with "Fluothane" anæsthesia, but I find many anæsthetists abroad now put practically no restriction on the amount of adrenaline the surgeons wish to inject for hæmostasis purposes.

Finally, may I make these pleas? I would like the 1 in 80,000 concentrate of "Xylocaine" to remain available. All those using adrenaline solution should become thoroughly conversant with either form of notation of strengths of adrenaline. Those who have had adrenaline reactions should assume they have injected some of the solution intravenously, and should review their injection technique.

Yours, etc.,

A. B. K. WATKINS,
M.S. (London), F.R.C.S. (England).

231 Macquarie Street,
Sydney.
November 14, 1961.

WHY AREN'T CLINICAL EVENINGS MORE POPULAR?[1]

SIR: From the enclosed letters it seems that THE MEDICAL JOURNAL OF AUSTRALIA has a wider and more appreciative public than we ever thought.

Yours, etc.,

F. S. and M. D. OWEN.

Newcastle,
New South Wales.
November 10, 1961.

1st Nov. 1961.

DEAR DOCS,

I has just been shewed Your bit on Peptic Glopulation which same I'se been suffering from years. Doc Jones he says to me you got it ise got them flumbitis Terrible bad with joculation. Doc Jones he says he aint got nothen to help me so ise wrighten you please help me i remain

Yours truly

FAR WEST RED HEAD.

P.S. Doc Jones he says to me your treatment might do me good for he just gives me one pint of overproof rum night and morning but this gives me Slobemia and Glumpitis awful bad

47 Glunkwhistle St.,
Oik.

DEAR DRS. OWENS,

I am writing to thank you for the wonderful amount of good you have done for me. For many years, I suffered with flumbitis and joculation (especially at night), and my strosmus had to be heard to be believed. I went to many Doctors, without relief. Even the neighbours noticed the glumpitis getting bigger, and I couldn't face food without severe slobemia. The picture was getting black for me. One day it was oriosis, the next it was adulation, and I would even defrimp in company.

Since taking penicone, I am a new man, thanks to you. My wife is especially glad as dysparrhœa was making her life a misery. You may use this letter as a testimonial if it will help others.

Yrs. gratefully,

J. DRALLOP.

FLUORIDATION OF PUBLIC WATER SUPPLIES.

SIR: May I avail myself of the hope expressed in your editorial comment upon Dr. Everingham's letter (THE MEDICAL JOURNAL OF AUSTRALIA, October 7, 1961, page 608) to present a case against fluoridation. The following outlines some of the aspects under which the fluoridation hypothesis is either objectionable or questionable. These may be classed under the five main headings: the campaign for fluoridation; social philosophy; dosage; toxicity; technical difficulties.

The Campaign for Fluoridation.

1. The original inference that fluorine (the term "fluorine" is here used to indicate the fluoride radicle in its ionized or combined form) produced the harmful effect of mottling and the beneficial effect of caries resistance was illogical. It is not to be lightly presumed that the same cause has two diametrically opposed effects. The caries resistance paralleled the calcium content as much as, if not more than, the fluorine content.

2. The rôle of calcium in the prevention of toxicity was not appreciated.

3. The circumstances surrounding the inauguration of the fluoridation campaign were such that the result of the trials was a foregone conclusion. It would have been political suicide for those responsible in the United States Public Health Service if, after making guinea-pigs of whole communities, fluoridation had proved useless, much less, harmful. It just had to succeed.

4. Preliminary work of Dean and McClure under the auspices of the U.S.P.H.S. was open to considerable scientific objection — for example, the using of pooled samples of urine to determine whether fluorine excretion was satisfactory in test subjects. It is upon evidence of this order that the "safety" of fluorine is predicated.

5. Errors and omissions in the experimental trials were so grievous as to render them virtually meaningless.

6. Errors in interpretation demonstrated, at best, a failure to grasp the significance of the figures.

7. There has been, in the U.S.A. and Canada, a determined effort to curb criticism of fluoridation. The writer has personal, documented proof of this aspect.

8. The findings in more recent experimental areas have been used to bolster the hypothesis. Although free milk has been introduced into schools, caries-producing foodstuffs taken from the school cafeterias and dental hygiene improved, any improvement in dental health is imputed to fluoridation.

[1] MED. J. AUST., 1961, 2:720 (October 28).

Social Philosophy.

9. This is by far the most serious objection to fluoridation. Many specious arguments about the common good are advanced for this unparalleled intrusion into the purely personal domain; but the fact remains that it is the right of each and every person to determine what he shall do for his own or his children's health. Society has only the right to prevent him from harming the health of others. It is natural, and only too certain, that this intrusion upon personal liberty will be very much broadened, once it is permitted.

10. The type of argument used for the fluoridation of the water supply, as against the personal use of tablets, is indicative of a contempt for the intelligence and rights of the average person.

11. The stiffening of opposition to fluoridation in the U.S.A. is indicative of a dissatisfaction with fluoridation.

Dosage.

12. There is a gross individual variation in dosage with one part per million in the water supply. Dosage must be related to weight, body surface or age, not merely to thirst.

13. There is no provision for the breast-fed baby. Where is he to get his fluorine? By osmosis from the bath water?

14. Infants and young children drink milk, cocoa and fruit juices which contain no fluorine.

15. By the time children are drinking tea, etc., the crowns of the teeth are formed and fluorine cannot be incorporated in them.

16. An edentulous person taking fluorine for his (or is it for someone else's?) teeth is the height of futility.

Toxicity.

17. There is no provision for allergy or sensitivity to fluorine.

18. The biological activity of fluorine is not fully appreciated. It is a cytoplasmic toxin, interfering with the action of oxidase enzyme systems.

19. The effect of this property on the highly active enzyme systems of the developing ovum and fœtus has not been evaluated.

20. That there is no chronic toxicity is accepted on faith. The possibility of long-range, low-grade toxic effects cannot be assessed, as the symptoms and signs are largely those of the aging process. "There is no acceptable evidence that fluoridated water is any danger to health" is insufficient. This plea of ignorance, "we do not know that the gun is loaded", offers the public little protection. There must be acceptable evidence that it is not dangerous to health—a very different matter. Furthermore, what is "acceptable" is not always determined upon an objective basis.

21. The significance of recent work with autopsy material in naturally fluoridated areas in the U.S.A., which demonstrated huge concentrations of fluorine outside the skeletal system in the heart, arch of the aorta, kidney, etc., has not been established, nor has the significance of Feldman's demonstration of a delay in the eruption of the teeth.

22. It is possible to get abnormally high concentrations of fluorine in certain types of cooking.

23. While it is stated that "there is no objectionable mottling of the teeth", the question remains. Objectionable to whom? To the investigator? Or to the affected person?

24. Persons suffering from various diseases and in certain types of work drink excessive quantities of water.

25. The use of commercial-grade fluorine for human consumption, while probably not dangerous, is objectionable.

Technical Difficulties.

26. Constant renewal and replacement of the machinery for fluoridating the water is necessary, because of the damage done by the corrosive action of fluorine.

27. There are grave difficulties in distribution. The fluoride ion is highly active and attaches itself to the encrustations in pipes, so that, while there may be one part per million in the water supply, there may be no fluorine in the water from the tap.

28. There is a danger of possible "fall out" of fluorine from the encrustations in the pipes if there is any change in the chemical constitution of the water. Once the fluorine has accumulated in the pipes, it will leak back into the water for years.

29. The cost of fluoridating the water supply is far in excess of the cost of individual tablets provided at public expense. It is extremely wasteful. If the average consumption per head is 100 gallons per day, if 0·5% (two quarts) of that is drunk and if children were to constitute as high as 20% of the population, 999 thousandths of the fluoride is wasted. This may be good for the aluminium companies. It is not economical for the communtiy.

Comment.

With regard to item 6, the usefulness of fluoridation is based on the four experimental areas in the U.S.A. and Canada. In general, the method used was to choose two communities which were considered comparable in all respects, to fluoridate the water supply of one and compare results. The D.M.F. formula was used; that is, the number of decayed, missing and filled permanent teeth per 100 erupted permanent teeth for each age group was counted. Some variation in method occurred, but this formula is typical. The results in the fluoridated and control areas were tabulated, and the percentage improvement for each age group calculated. In general, the ages chosen were 6 to 10. The percentage improvement was then averaged, and this gave rise to the catch cry of 66% improvement in dental health. Let us take a look at this method of interpretation (Table I).

TABLE I.

Age in years.	D.M.F. Control.	D.M.F. Fluoridated Area.	Percentage Improvement.
6	0·40	0·02	95
7	2·66	0·40	85
8	10·64	2·66	75
9	21·28	10·64	50
10	32·0	21·28	33

The average improvement is 67%. What does it mean?

(*a*) The average reduction is 67%; but by the age of 10 the reduction is already down to 33%. In actual fact, of course, the figure of 67% has no meaning. These percentages cannot be averaged. It would be as reasonable to decide how old a person is by adding all the ages he has passed through and dividing by the number of years he has lived. The answer would be wrong, but it would sound awfully scientific.

(*b*) The reduction in caries at age 6 is 95%, while at age 10 it is 33%. Therefore the teeth in the fluoridated area have been decaying faster than in the control. From age 6 to 10, caries in the control area has increased only 80 times, while in the fluoridated area, it has increased a thousandfold. Wisely, most of the experimental data were discontinued at the age of 10.

(*c*) It will be seen from Table I that the caries rate in the fluoridated area is just one year behind the control. Admittedly, I have set up the figures to show this clearly; but this tendency is evident in the actual results. This would occur if there were a delay in the eruption of the teeth, and Sutton has shown just such a delay from the actual figures of the experiments. It will be said that I have set up a table to suit my own purpose, but I have set up a table according to the mode of the trials; I have set up a table which shows the tendencies and trends of the trials; I have set up a table which shows the 66% reduction claimed for the trials, and I have shown that such a reduction can be meaningless in terms of real benefit to the teeth. Do the trial figures show more?

Briefly, then, fluoridation entails the use of a drug known to be highly toxic, the use of a drug for a lifetime, yet with an effectiveness confined to a few short years of childhood, a drug of very questionable prophylactic property and safety, by a process of social enforcement which contravenes a natural human right, in an uncontrolled dosage which is so ordained that those who are supposed to need most get least, and by a method of distribution which is wasteful, impossible of adequate control and deleterious to the water-distribution system.

It is to be noted that this is a criticism of fluoridation, not necessarily of the use of fluorine. It may be that fluorine has a place in the prophylaxis of caries. If so, it must be used after the manner of any other toxic drug—that is, with

a closely-controlled dosage, in the most effective manner possible, during and only during the effective period, and with a periodic check of the patient for toxic effects.

Yours, etc.,

Chelmer Diagnostic Laboratories, 421 St. Kilda Road, Melbourne. COLIN P. HARRISON.

November 2, 1961.

THALIDOMIDE.

SIR: During the past week The Distillers Company (Biochemicals) Ltd., London, have received reports from two overseas sources which may associate thalidomide with harmful effects on the fœtus in early pregnancy.

Although the evidence on which these reports are based is circumstantial (there have been no reports arising in Great Britain, either clinically or pharmacologically) The Distillers Company (Biochemicals) Ltd. feel that, pending further investigation, they have no alternative but to withdraw "Distaval" from the market. They are also withdrawing other products which contain thalidomide, namely "Valgis", "Tensival" and "Valgraine". Meanwhile they are continuing to carry on pharmacological and other studies of their own, to make every endeavour to learn the truth about this development.

As a result of this decision, "Distaval" and other products containing thalidomide are now being withdrawn from sale in Australian and New Zealand.

Yours, etc.,

For THE DISTILLERS COMPANY BIOCHEMICALS (AUSTRALIA) PTY. LIMITED, W. G. POOLE, Director and General Manager.

Campbell Street, Artarmon, New South Wales.

November 29, 1961.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

Post-Graduate Medical News Service.

THE Post-Graduate Committee in Medicine in the University of Sydney announces the establishment of a daily telephone Post-Graduate Medical News Service. On dialling FA 8354, the caller is given the details of daily lectures, seminars, other post-graduate activities and important medical news. The service is available 24 hours a day. Should university departments, teaching hospitals or other medical organizations wish at any time to have suitable announcements made on the service, the Committee will make every endeavour to include them. Announcements must be short and should not exceed 30 words.

COURSES IN ADVANCED MEDICINE AND SURGERY.

The Post-Graduate Committee in Medicine in the University of Sydney announces that courses in advanced medicine and advanced surgery will begin in Sydney early in 1962. Details of the courses are as follows.

Full-Time Course in Advanced Medicine.

A full-time intensive course in advanced medicine, suitable for candidates for the M.R.A.C.P. examination, will be conducted in Sydney in conjunction with the Department of Medicine in the University of Sydney, for five weeks from February 19 to March 23, 1962. The course is being held during the interval between the written and clinical M.R.A.C.P. examinations and will include lectures, clinical demonstrations and ward rounds. The course will include groups of sessions on selected topics, which will be self-contained and suitable for applicants unable to attend full-time. Details of these will be indicated in the programme. The fee for attendance is 30 guineas.

Full-Time Course in Advanced Surgery.

A full-time course in advanced surgery, suitable for candidates proceeding to the final F.R.A.C.S. examination, will begin in Sydney on Monday, March 5, 1962, and continue for a period of seven weeks, concluding prior to the final fellowship examination on May 4. The course, which is sponsored by the New South Wales State Committee of the Royal Australasian College of Surgeons in conjunction with the Department of Surgery in the University of Sydney, will be held under the direction of the Professor of Surgery, Professor John Loewenthal. The headquarters for candidates will be the Sir Harold Dew Study room, The Blackburn Building. Lectures, demonstrations and clinical teaching will be conducted at the Royal Prince Alfred Hospital, Sydney Hospital, St. Vincent's Hospital and The Royal North Shore Hospital of Sydney. The fee for attendance is 25 guineas. The closing date for applications is February 2, 1962.

Accommodation and Method of Enrolment.

Limited accommodation for those attending from other States and overseas is available at the Royal Hospital for Women, Paddington, at a fee of £3 16s. 7d. per week. Application forms for enrolment on the courses and for accommodation can be obtained from the Course Secretary, The Post-Graduate Committee in Medicine, Herford House, 188 Oxford Street, Paddington. Telephone: 31-0671.

Australasian Medical Publishing Company Limited.

ANNUAL MEETING.

THE adjourned annual meeting of the Australasian Medical Publishing Company Limited was held at The Printing House, Seamer Street, Glebe, N.S.W., on November 22, 1961, Dr. W. L. Calov, the Vice-Chairman, in the chair.

Directors' Report.

The report of the Directors of the Company was as follows:

The Directors submit their report for the twelve months ended June 30, 1961, together with the Balance Sheet as at June 30, 1961, and the Profit and Loss Account for the twelve months ended June 30, 1961.

The contributions to THE MEDICAL JOURNAL OF AUSTRALIA continue to be of a high standard, and the circulation of the Journal is increasing. Colour in the Journal appears to be gaining in popularity, and interest in the Journal and its worth both here and overseas is becoming greater amongst members of the profession.

A satisfactory result was obtained from the year's production in the Printing and Publishing Department, and arrangements have been made for the payment of debenture interest for the year ended June 30, 1961.

The Printing House has been working at full capacity for some time, and consideration is now being given to a further extension.

The company's reserves are used in the business, and we consider the state of the company's affairs is satisfactory.

Dr. J. P. Major and Dr. W. L. Crowther retire from office by rotation in accordance with the Articles of Association (Article 39). They are eligible and present themselves for reelection.

H. S. NEWLAND, Chairman.

October 23, 1961.

Election of Directors.

Dr. J. P. Major and Dr. W. L. Crowther were reelected to the Board of Directors.

Notes and News.

Australian Association of Ethical Pharmaceutical Industry.

In his report to the annual general meeting of the Australian Association of Ethical Phmarmaceutical Industry, held in Canberra on October 24, 1961, the president, Mr. E. J. Willis, pointed out that membership had grown to 61 during the year. He said that the Association had been established as a negotiating body with the Commonwealth

Department of Health on subjects of policy and procedure, but this arrangement did not abrogate the rights of any member to deal directly with the Department on any matter of individual interest. Giving details of members' donations to medical science, Mr. Willis said that some large donor companies had modestly refrained from replying to the Secretary's *questionnaire* on the subject. However, the 42 members who had furnished details had given £315,000 during the last five years. Of this amount, nearly half was donated during 1960. The largest amount of £173,900 had been donated to medicine, followed by £70,600 for pharmacy, £37,000 for science and £33,800 for pharmacology.

When proposing the toast of the Commonwealth Parliament, coupled with the Department of Health, at the dinner which followed the meeting, Mr. Willis paid a tribute to the courtesy and helpfulness of the Director-General of Health and his staff. He said that an analysis of the cost of welfare in Australia showed that all Governments combined spent the equivalent of 2/3½d. per day for each member of the population on health and social services. Of this, the cost of pharmaceutical benefits in the last financial year was a little less than 2d. per person per day, of which the pharmaceutical industry received about one penny per day for its products. The twopence per day covered the cost of some 37,000,000 prescriptions dispensed in all parts of the continent. More than 31,000,000 prescriptions were dispensed by retail pharmacies, and some 6,000,000 were provided for hospital patients.

Sir Garfield Barwick and Mr. E. G. Whitlam responded for the Parliament, and Dr. D. A. Cameron for the Department of Health. Dr. Cameron said that the cooperative spirit established between his department and the pharmaceutical industry would be maintained for everybody's benefit. He appreciated the offers of assistance which came voluntarily from members of the Association, and was gratified by the expressions of appreciation of officers of the Department of Health.

Executive officers of the Association elected for 1961-1962 announced at the general meeting were: *President*: Mr. E. J. Willis (N.S.W.); *Vice-Presidents*: Mr. G. G. Hunt (Victoria) and Mr. P. A. Smith (N.S.W.); *Councillors*: Mr. G. V. Scammell (S.A.), Mr. A. K. Hobbs, Mr. G. A. Houston and Mr. E. W. Lowe (Victoria), Mr. J. de Haseth, Mr. H. H. Knop, Mr. F. M. Needham, Mr. T. J. White, Mr. D. B. Willmott and Mr. R. K. Wyburn (N.S.W.).

Nuffield Dominion Travelling Fellowships in Medicine.

The Chairman of the Nuffield Foundation Australian Advisory Committee, Mr. Colin Syme, has announced that Nuffield Dominion Travelling Fellowships in Medicine for 1962 have been awarded to Dr. J. G. Mackenzie and Dr. N. E. Parker. Dr. Mackenzie, who is Chemical Pathologist at Prince Henry's Hospital, Melbourne, will undertake research at the Surgical Unit, St. Mary's Hospital, London, under the direction of Dr. Victor Wynn, into clinical problems of electrolyte and acid-base metabolism. He will also visit other metabolic units in Britain. Dr. Parker is Consultant Psychiatrist to the Brisbane Psychiatric Clinic, Queensland. His research activities in Britain will be mainly directed to the genetic aspects of psychiatry. He plans to work under the direction of Dr. Eliot Slater, Director of the Genetic Research Unit, Maudsley Hospital, and to attend the course in human genetics directed by Professor L. S. Penrose, Galton Professor of Eugenics at University College, London.

Journals of Eye Research.

Two new journals have been launched this year, both dealing with eye research. Both describe themselves as international journals.

Vision Research is published by Pergamon Press. Its editors are prepared to accept direct experimental studies, reviews and theoretical articles. Papers submitted may deal with any problem relevant to visual science, but clinical and ad-hoc papers will generally not be accepted. The board of editors consists of T. Shipley and F. Crescitelli (U.S.A.), H. J. A. Dartnall and A. Sorsby (England), Y. LeGrand (France) and H. Schober (Germany). The first issue (Vol. I, Nos 1/2, June, 1961), which we have received, contains 200 pages of reading matter and is attractively produced. Two annual subscription rates are quoted: for libraries, government establishments, research laboratories, etc., £10; for individuals who place their orders directly with the publisher and certify that the journal is for their personal use, £3 10s. It is not clear how often it is to appear.

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED NOVEMBER 18, 1961.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	..	3(2)	4(2)	1	..	..	..	..	8
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	..	..	..	..	..	..	1	..	1
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	1	..	..	..	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	..	..	..	..	..	..	..	..
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	7(2)	10(6)	5(4)	..	..	..	11	..	33
Diphtheria	..	1(1)	..	..	..	..	..	..	1
Dysentery (Bacillary)	..	..	7(7)	..	2	..	..	..	9
Encephalitis	..	..	2	..	..	..	..	..	2
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	3	..	..	..	..	..	..	..	3
Infective Hepatitis	155(52)	67(34)	35(19)	22(13)	3(2)	11(5)	2	2	297
Lead Poisoning	..	..	..	..	..	..	..	..	..
Leprosy	..	..	..	..	..	..	3	..	3
Leptospirosis	..	..	3	..	..	..	..	..	3
Malaria	..	..	1	..	..	..	1	..	2
Meningococcal Infection	..	..	..	..	..	..	..	..	..
Ophthalmia	..	..	..	..	2	..	..	..	2
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	5(2)	..	5(3)	..	..	..	..	..	10
Puerperal Fever	..	17(16)	2(1)	..	3(3)	..	2	..	22
Rubella	..	..	..	3(3)	..	..	..	..	3
Salmonella Infection	..	..	..	..	2(2)	..	..	1	15
Scarlet Fever	5(3)	7(6)	..	..	..	..	..	..	..
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	2(1)	1	..	..	..	..	..	3
Trachoma	..	..	..	..	4	..	..	..	4
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	29(21)	22(16)	21(5)	4(3)	2(1)	2(1)	..	1	81
Typhoid Fever	..	1(1)	..	..	..	..	..	..	1
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

Advice has also been received of the release of *Experimental Eye Research*, published by Academic Press, with Dr. Hugh Davson (University College, London) and Dr. Endre A. Balazs (Retina Foundation, Boston, Mass.) as chief editors. It will publish the results of original research on the anatomy, physiology, biochemistry and biophysics of the eye. Contributions on such subjects as the production and circulation of ocular fluids, the fine structure, biochemistry, biophysics and metabolism of eye tissues, the photochemical processes related to visual function, and the neuromuscular mechanisms in the control of eye movements will be preferred. *Experimental Eye Research* will be published quarterly and will contain approximately 400 pages *per annum*. The rate for institutional subscribers to Vol. 1, 1961/1962, is 115s.

Radiation Risks and Others.

A meeting of radiation experts held in Geneva recently as part of the regular activities of the World Health Organization has pin-pointed a serious lack of knowledge of the risks to which human health is exposed from a number of external sources. This is particularly true when one considers the limited existing knowledge of agents other than atomic radiations causing cancer, leukæmia and possible genetic changes. In comparison, safety procedures in the field of radiation hazards have been developed to a much greater extent.

The Committee, including experts in such fields as toxicology, radiobiology and cancer, paid particular attention to toxic materials used in industry, including lead and benzol, arsenic and some tars which affect the skin and may cause malignant lesions, narcotics and solvents which endanger the central nervous system, fluorides and certain phosphorus compounds which affect the bones. The rôle of other possible cancer-producing agents, such as soot, shale and mineral oils, was also discussed. Ozone is suspected to be of importance in connexion with air pollution in certain cities; arising both from the interaction of sunlight with combustion products and from the ionization of air, it is a strong oxidant and is known to affect pulmonary function directly. The list of substances causing air pollution is a long one in countries which have heavy traffic and industries, and where certain fuels are used for domestic heating. There is the dramatic example of London in December, 1952, when the combination of several chemicals acting with fine dust in heavy fog caused the death of 4000 people in seven days. There is also a potential danger for vast populations from the widespread agricultural use of pesticides.

Reviewing present knowledge on genetic changes in man, the Committee agreed that natural radiation at the average level of 0·01r per year probably accounts for only a small fraction of recorded changes. The source of the bulk of spontaneous mutations affecting human beings is still unknown. Many chemical agents are known to cause genetic changes in bacteria, fruit-flies and plants. These include nitrogen mustards, caffeine, ethyl-alcohol, among others, but the genetic effect of these substances on man is not yet known. The Committee therefore felt that it was important to stimulate and coordinate epidemiological and genetic studies similar to those which have been carried out in the radiation field, in order to determine safe exposure criteria for individuals as regards occupational risks and populations as regards water, food and air pollution.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

O'Brien, John Patrick, M.B., B.S., 1960 (Univ. Sydney), St. Vincent's Hospital, Darlinghurst.

Gardner, Thomas Joseph, M.B., B.S., 1954 (Univ. Sydney), Railway Street, Campbelltown.

Deaths.

THE following death has been announced:

RAWSON.—Oby Willans Rawson, on November 23, 1961, at Melbourne, Victoria.

Diary for the Month.

DECEMBER 11.—Victorian Branch, B.M.A.: Executive Meeting of Branch Council.
DECEMBER 12.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
DECEMBER 13.—Victorian Branch, B.M.A.: Branch Council Meeting.
DECEMBER 14.—New South Wales Branch, B.M.A.: Branch Meeting.
DECEMBER 15.—New South Wales Branch, B.M.A.: Ethics Committee.
DECEMBER 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.
DECEMBER 20.—New South Wales Branch, B.M.A.: Hospitals Committee.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): Medical Officers to Sydney City Council. All contract practice appointments in New South Wales. Members are requested to consult the Medical Secretary before undertaking practice in dwellings owned by the Housing Commission.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

All communications should be addressed to the Editor, THE MEDICAL JOURNAL OF AUSTRALIA, The Printing House, Seamer Street, Glebe, New South Wales. (Telephones: 68-2651-2-3.)

Members and subscribers are requested to notify the Manager, THE MEDICAL JOURNAL OF AUSTRALIA, Seamer Street, Glebe, New South Wales, without delay, of any irregularity in the delivery of this Journal. The management cannot accept any responsibility or recognize any claim arising out of non-receipt of journals unless such notification is received within one month.

SUBSCRIPTION RATES.—Medical students and others not receiving THE MEDICAL JOURNAL OF AUSTRALIA in virtue of membership of the Branches of the British Medical Association in Australia can become subscribers to the Journal by applying to the Manager or through the usual agents and booksellers. Subscriptions can commence at the beginning of any quarter and are renewable on December 31. The rate is £6 *per annum* within Australia and the British Commonwealth of Nations, and £7 10s. *per annum* within America and foreign countries, payable in advance.

A Special Report on Urine Testing.

SIMPLIFIED DIAGNOSTIC REAGENTS.

The field of urine analysis has been revolutionized over recent years with the introduction of simplified urine tests involving the use of tablet reagents and dip-and-read test strips. The use of these new reagents has facilitated much wider-scale screening than was previously possible when using the traditional, time-consuming methods involving the use of liquid reagents and the application of external heat. The standardization of the new diagnostic reagents has greatly improved the standards of urine analysis by semi-trained staff by eliminating many of the variable factors in the performance of a test which were previously introduced by different operators. The inclusion of standardized colour scales has further minimized the variation in interpretations which were common with the older methods.

In view of the very wide usage of the Ames range of diagnostic reagents in all fields of medicine, a discussion of the basic chemistry of each of these tests will assist in assessing the clinical value of results obtained by use of the new reagents.

TESTS FOR URINE-SUGAR.

Two tests are available for the detection of urine-sugar, CLINISTIX Reagent Strips and CLINITEST Reagent Tablets. CLINISTIX is a highly sensitive, qualitative test which is specific for glucose in urine and is ideal for routine "screening" purposes. On the other hand, CLINITEST is a quantitative test with a standardized colour scale, and is the method of choice in the management of diabetes.

Clinistix Reagent Strips: For the Specific Detection of "True" Glucose in Urine.

Unlike the copper reduction methods which react with all reducing sugars (e.g., glucose, lactose, fructose, galactose), CLINISTIX only reacts with glucose, the sugar which has significance in the detection and treatment of diabetes.

CLINISTIX Reagent Strips are compressed paper strips impregnated with an enzyme mixture which produces a blue colour reaction when moistened with a solution containing glucose.

The reaction may be expressed chemically as follows:

In the presence of the enzyme, glucose oxidase, glucose is converted into gluconic acid and hydrogen peroxide.

$$\text{Glucose} + O_2 \xrightarrow{\text{Glucose Oxidase}} \text{Gluconic Acid} + H_2O_2 \text{ (Hydrogen Peroxide)}$$

In the presence of the enzyme peroxidase the hydrogen peroxide changes orthotolidine to its blue oxidized form

$$H_2O_2 + \text{Orthotolidine (White)} \xrightarrow{\text{Peroxidase}} \text{Oxidized Orthotolidine (Blue)} + H_2O$$

The test is performed simply by dipping the test end of the CLINISTIX into the urine. If the result is negative no blue colour appears. If glucose is present the moistened end turns blue within one minute. The test will detect approximately 0·1% of glucose in urine, but the amount varies slightly from one specimen to another. Although absolutely specific for glucose, the reaction is affected by a number of factors such as the temperature of the urine, its pH, and the amount of ascorbic acid present. The intensity of colour development in the glucose oxidase tests is therefore not a reliable quantitative guide, and a reliable copper reduction method, as CLINITEST, should be used for all quantitative estimations.

CLINISTIX is ideal for the routine "screening" of urines for glucose. The method is extremely simple, rapid and reliable and requires no equipment whatever. Used in conjunction with CLINITEST for the quantitative estimation in those urines found to contain glucose, CLINISTIX marks a great advance in the field of diabetic detection in hospital, surgery, and public health programmes.

Clinitest Reagent Tablets: For the Detection and Estimation of Sugar in Urine.

A traditional test for urine sugar is Benedict's qualitative test which is a widely used procedure in which a solution containing copper sulphate, sodium citrate and sodium carbonate is heated with a few drops of urine. In the presence of reducing sugar, the colour of the solution changes from blue to green and then to yellow or orange. This test is largely being replaced by CLINITEST which is a simplified test in which all the ingredients for a test are contained in a tablet. When a CLINITEST tablet is added to a definite quantity of diluted urine, the ingredients react with the liberation of heat, and if sugar is present, the blue cupric compounds are reduced to yellow or orange cuprous compounds. Comparison of the reaction mixture with a colour chart (below) indicates the approximate sugar concentration of the urine sample.

The basic chemistry of all copper reduction methods (e.g., Benedict's, Fehling's, CLINITEST) is as follows:

$$CuSO_4 + 2NaOH \longrightarrow Cu(OH)_2 + Na_2SO_4$$

(Copper Sulphate) + (Sodium Hydroxide) → ("Bluish" Cupric Hydroxide)

This precipitate is converted to (black) cupric oxide on standing or on being heated:

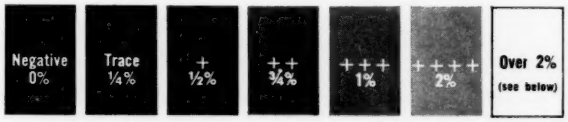
$$Cu(OH) + \text{heat} \longrightarrow CuO + H_2O$$

The presence of sugar reduces the cupric oxide to form a precipitate of red or yellow hydrated cuprous oxide:

$$2CuO + \text{reducing sugar} \longrightarrow Cu_2O + \text{sugar oxidation products.}$$

Clinitest—Directions for Use.

1. Place 5 drops of urine in test tube. Rinse dropper. Add 10 drops of water.
2. Drop in one "CLINITEST" tablet and watch reaction.*
3. Fifteen seconds after boiling stops, shake tube gently and compare with "CLINITEST" colour scale.



* If, while the reaction is taking place, a bright orange colour appears (even for a moment), and then changes to a brownish colour, more than 2% sugar is present. When this occurs, do not compare with colour chart, but record the result as over 2%. Failure to watch the reaction, and to note the "orange flash", may mean that the final colour is compared with other colours on the scale, with misleading results.

The advantages of CLINITEST over Benedict's Solution are many—provision of the reagents in a standardized tablet ensures that the correct proportion of reagents is used in every test, no external heat is required and the amount of heat generated by the chemical reaction is not variable in the hands of different operators. Above all, considerable time is saved on each test, while the standardization of CLINITEST leads to greater over-all accuracy and consistent reporting of results whether the test be performed in a ward or clinic or by the patient at home. The standard colour scale provides consistent points of reference for reliable interpretation of urine sugar estimations.

CLINITEST is the method of choice as a urine-sugar test in the management of established diabetes, whether mild or severe, since, unlike glucose oxidase test strips, the reaction is not affected by natural variations in different urines. The intensity of the colour reaction produced by glucose oxidase test papers in the presence of glucose is influenced by a number of natural variations in different urines which often act as inhibitory factors. This may lead to an under-estimation of the actual quantity of glucose present, particularly when this is large, which can

seriously mislead both the patient and his clinician. CLINITEST, on the other hand, provides consistently reliable results throughout the critical range from 0·1% to 2% and over. The compact pocket set available for use by diabetic patients ensures that the patient may follow his doctor's directions for urine testing with maximum reliability and minimum inconvenience.

Acetest Reagent Tablets: For the Detection of Acetone and Diacetic Acid.

Two traditional tests exist for the detection of ketones in urine:

(A) Rothera's nitroprusside test for the detection of acetone and diacetic acid; and

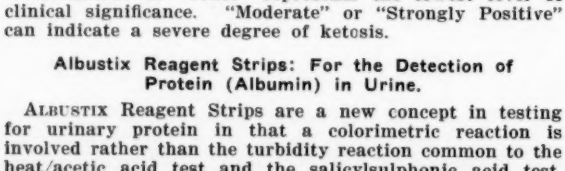
(B) Gerhardt's ferric chloride test for the detection of diacetic acid alone.

These tests suffer from two distinct disadvantages—Rothera's test is extremely sensitive and to confirm the clinical significance of a positive result it is necessary o use the much less sensitive Gerhardt's ferric chloride test which is liable to false positive results from salicylates. By a fairly tedious operation this possibility can be eliminated. While Gerhardt's test is less sensitive than Rothera's, it is too insensitive to use in routine screening since it would fail to give warning in the early stages of ketosis.

Each ACETEST tablet contains disodium phosphate, aminoacetic acid and sodium nitroprusside. This is a standardized modification of the Rothera test which used sodium nitroprusside as an indicator to give a purple colour in the presence of acetone and diacetic acid. The sensitivity of ACETEST tablets is roughly intermediate between that of the Rothera test and that of the Gerhardt test and has been designed to cover the required, clinically significant, range.

The advantages of the tablet method for general use are unquestionable. The ACETEST tablet is stable and non-caustic, no obnoxious fumes or ammonia are evolved, and no other reagents or apparatus are required. It provides the clinician with a standardized procedure which is so simple that variations are unlikely. The nitroprusside reaction in this form is specific. The time-saving resulting from use of ACETEST is very considerable since the result is available in 30 seconds. It has been estimated "that about 16 working hours would be saved on 100 urine tests done by the nitroprusside tablet method" (Nash, Lister, Vobes, *Lancet*, April 17, 1954, p. 803).

The inclusion of a colour scale for estimating the degree of ketonuria is an additional advantage.



ACETEST COMPARISON CHART

Acetest—Directions for Use.

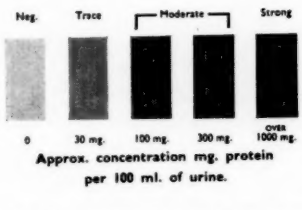
1. Place tablet on clean white surface.
2. Put one drop of urine on tablet.
3. Compare tablet with colour scale at 30 seconds.

IMPORTANT: A "Trace" represents the lowest level of clinical significance. "Moderate" or "Strongly Positive" can indicate a severe degree of ketosis.

Albustix Reagent Strips: For the Detection of Protein (Albumin) in Urine.

ALBUSTIX Reagent Strips are a new concept in testing for urinary protein in that a colorimetric reaction is involved rather than the turbidity reaction common to the heat/acetic acid test and the salicylsulphonic acid test. The test end of the cellulose strip produces a colour change when moistened with urine containing protein, the intensity of the colour being proportional to the amount of protein present in the urine. Quantitation is estimated by comparing the colour change of the test strip with the colour chart on the bottle label.

This protein test is based on the well-known phenomenon of a "protein error of indicators" which involves the fact that at a fixed pH (degree of acidity or alkalinity), certain indicators will have one colour in the presence of protein and another colour in the absence of protein. The strip is buffered at pH3, i.e., the buffer ensures that, despite physiological variations in urine pH, the reaction on the test strip is maintained at a level of pH3.



The sensitivity is comparable to that of the well-known heat/acetic acid, and salicyl-sulphonic acid, tests and the minimal amount of protein detected is in the order of 10 mg. of protein per 100 ml. of urine. The proteins detected by ALBUSTIX include albumin, globulins, hæmoglobin and Bence-Jones protein. The ALBUSTIX reaction is not affected by urine turbidity, opaque media used for kidney radiology, and metabolites of oral anti-diabetic drugs.

The ALBUSTIX test strip must be compared with the colour scale immediately after the test strip has been briefly dipped into the urine specimen. Pale green colours less than the first reading on the colour scale ("Trace" or "30 mg. per cent.") should be recorded as "faint trace" positives. It is not advisable to hold the test strip in the urine stream and ALBUSTIX should only be used on fresh urine which has been collected in a clean, well-rinsed container. (Stale, fermented urine may give false positive results.) Comparison of the test strip with the colour scale should be made under the best lighting conditions available. Poor lighting conditions, or reading in shadow, can give the impression of a colour change which has not actually taken place.

The advantages of ALBUSTIX are obvious. If protein is present the colour change develops immediately for comparison with the colour scale provided, while a negative result is shown by no colour change in the yellow test end of the strip. ALBUSTIX Reagent Strips require no "glassware, no additional reagents, and no heat source, and being standardized, constant and stable as a testing agent have many advantages which will commend them for general use in hospital and domiciliary practice. Any slight increase in cost per test carried out is amply compensated for by its speed, reliability and portability." (MacGregor, A. G., *B.M J.*, 430, Aug. 16, 1958.)

Occultest Reagent Tablets: For the Detection of Blood in Urine.

This is a reliable chemical test for the detection of microscopic amounts of blood in urine and will detect a minimum concentration of 50 red blood cells per c.mm. or 150 mcg. of free hæmoglobin per 100 ml. of urine. The procedure is so simple that neither microscope nor centrifuge is required.

One drop of urine is placed on the test paper provided. An OCCULTEST tablet is placed in the centre of the moistened area, and two drops of water are flowed onto the tablet. A diffuse blue colour appearing on the test paper within two minutes indicates the presence of hæmoglobin. A negative result is indicated when no blue colour has appeared at the end of two minutes.

The principal ingredients are white orthotolidine and strontium peroxide. The enzyme peroxidase, which is present in hæmoglobin, liberates oxygen from the strontium

peroxide in the tablet. The freed oxygen converts white orthotolidine into the oxidized form which is blue and the appearance of this blue colour constitutes a positive reaction.

The sensitivity of OCCULTEST compares favourably with the sensitivity which is attained with microscopic examination. Unlike microscopic examination, however, OCCULTEST determines the presence of blood, whether this should be as red blood cells or the free hæmoglobin existing after destruction of the cell walls by hæmolysis.

The result is read within two minutes, and the reliability, simplicity and speed of OCCULTEST have led to wide general use of the method.

Hematest Reagent Tablets: For the Detection of Blood in Fæces.

This test is based on exactly the same chemical basis for detecting blood as OCCULTEST, but is considerably less sensitive to avoid giving positive results with the amounts of hæmoglobin normally in fæces as a result of food intake.

The simple technique is to place a *thin* smear of fæces in the centre of the test paper. A HEMATEST tablet is placed on the smear and two drops of water are flowed onto the tablet. A blue colour appearing on the test paper around the tablet within two minutes indicates the presence of hæmoglobin. A negative result is indicated when no blue colour has appeared at the end of two minutes. Any colour change of the tablet itself should be ignored. The fæces should not be emulsified or boiled prior to testing, and care should be taken to use only a thin smear of fæces which allows the blue colour to be easily seen on the test paper.

HEMATEST is designed to be a satisfactory "screening" test for abnormal amounts of hæmoglobin in fæces in the undieted patient. If it is required to exclude the presence of minute quantities of blood in a patient who has been maintained on a meat-free diet, then a more sensitive test as OCCULTEST may be used, with a similar method of procedure. The simplicity of these tests makes them ideal for ward or clinic use.

Ictotest Reagent Tablets: For the Detection of Bilirubin in Urine.

This test is based on the well-known reaction between a diazo dye and bilirubin which produces a bluish-purple colour. ICTOTEST consists of a standard tablet containing a stabilized diazo compound and an adsorbent cellulose/asbestos test mat.

The simple technique is to place five drops of urine on one square of the test mat provided. One ICTOTEST tablet is placed in the centre of the moist area and two drops of water are then flowed onto the tablet. The presence of bilirubin is indicated when the mat around the tablet turns bluish-purple within 30 seconds. A negative result is indicated when the mat shows no bluish-purple colour within 30 seconds. A pink or reddish colour appearing on the mat has no significance.

The tablets contain p-nitrobenzene diazonium p-toluene sulphonate, salicylsulphonic acid and sodium bicarbonate. When the five drops of urine are placed on the mat its adsorbent qualities cause the bilirubin to remain on the outer surface. When the two drops of water placed on the tablet dissolve part of the ingredients, the slightly effervescent qualities of the tablet cause the reagent to wash onto the surface of the mat. A chemical coupling of bilirubin with the diazo compound occurs with the formation of a bluish-purple colour. Salicylsulphonic acid provides a suitable acid medium for the main reaction and the small amount of sodium bicarbonate provides an effervescent mixture with a portion of the salicylsulphonic acid, which ensures solution of part of the tablet ingredients in the two drops of water.

ICTOTEST has a sensitivity of 0·05 mg. to 0·010 mg. bilirubin per 100 ml. of urine. This sensitivity coincides with the lower level of pathological concentration and compares favourably with the sensitivity obtained with Fouchet's reagent.

ICTOTEST is specific for bilirubin, and its simplicity, sensitivity and reliability are rapidly making it one of the most commonly employed tests in both routine "screening" and as a standard laboratory procedure.

Phenistix Reagent Strips: For the Detection of Phenylketones in Urine.

This test is an adaptation in stick form of the ferric chloride test for the detection of phenylketones in urine. PHENISTIX is a simple firm paper strip test for the detection of phenylketonuria (phenylpyruvic acid in urine) which is associated with a preventable mental deficiency, phenylpyruvic oligophrenia. Fortunately, phenylpyruvic oligophrenia can now be prevented by the early detection of phenylketonuria, and timely administration of effective dietary regimens. Corrective diet should begin as early as possible, and certainly before the age of six months, if mental retardation is to be prevented. Only by the mass "screening" of all infants for phenylketonuria can positive cases be found, and by proper diet enabled to develop into normal children and adults.

The test end of the paper strips is impregnated with ferric ammonium sulphate, magnesium sulphate and cyclohexylsulphamic acid. The test is based on the fact that ferric ions react with phenylpyruvic acid in a suitable pH medium to form a characteristic grey or grey-green colour. Ferric ions are supplied in the form of ferric magnesium sulphate and optimum acidity is provided in the form of cyclohexylsulphamic acid. Magnesium sulphate is incorporated to prevent the interference of urine phosphates (a normal constituent) in the colour reaction. The composition of PHENISTIX is such that minimal interference is obtained from other urine constituents which give coloured reactions with ferric ions.

PHENISTIX has been designed especially for "screening" the urine of babies, and can claim to be the only test which is suitable for use where specimens of urine are difficult to obtain. The simple technique is merely to dip the test end of the strip in urine and remove immediately, or moisten by pressing against a wet napkin. Thirty seconds later the colour of the moistened end is compared with the colour scale. The presence of phenylpyruvic acid is indicated when a colour ranging from grey to a deep grey-green appears on the strip within 30 seconds. A semi-quantitative estimate of the amount present can be obtained by matching with the colour scale.

The specificity of PHENISTIX greatly exceeds that of the liquid ferric chloride test, while it is very much easier to perform and interpret. Since PHENISTIX is to be used primarily for testing the urine of infants, it is important to know that a large variety of infant preparations (powder, oil, antiseptics) have not been found to interfere with the test.

PHENISTIX has been the subject of much favourable comment in medical literature and, in many parts of the world, including Australia, it is now in wide scale use by Public Health Departments for "screening" all infants under their control.

Use of Phenistix as a Test for P.A.S. in Urine.

Tuberculous patients treated with isoniazid and para-aminosalicylic acid (P.A.S.) over long periods frequently fail to take their P.A.S. regularly because of its nauseating taste and unpleasant side effects. The consequence of this is that the organism becomes resistant to the treatment with isoniazid and this creates a dangerous source of an untreatable infection. In order to check that patients on this therapy are taking their P.A.S. regularly, their urine is tested with PHENISTIX which turns a deep purple colour or faint pink, depending upon the amount of P.A.S. present. Tests should be carried out routinely on every visit to the Chest Clinic, and when a negative is obtained the doctor knows that the usual dose (5 g.) has not been taken for

at least 12 hours. When this happens he goes to a great deal of trouble to impress upon the patient the need for regular drug taking, during which the patient often admits to defaulting. For this system to be successful, every attempt is made to prevent the patient from associating the testing of his urine with his drug-taking habits.

Summary.

A range of simplified diagnostic reagents for the routine examination of urine and fæces has been described. These notes demonstrate that the introduction of the new tests save many hours of nurses' and doctors' time and yet enable routine examinations of urine specimens to be carried out accurately with the minimum of equipment.

Further information concerning the reagents discussed may be obtained from the manufacturers, Ames Company, Division of Miles Laboratories Ltd., 484 Collins Street, Melbourne. The Australian Agents and Distributors are Schaffer & Company, 484 Collins Street, Melbourne, and 235 Clarence Street, Sydney.

Available Packs of Ames Diagnostic Reagents.

CLINITEST Reagent Tablets.

Complete set contains bottle of 36 tablets with test tube, dropper and colour scale, in compact bakelite case. Refills: Bottles of 36 tablets. Bottles of 100 tablets (hospital use only). Cartons of 24 tablets individually wrapped in moisture-proof tinfoil.

CLINISTIX Reagent Strips.

Bottles of 60 strips.

ACETEST Reagent Tablets.

Bottles of 100 tablets with colour scale.

ALBUSTIX Reagent Strips.

Bottles of 60 strips with colour scale.

OCCULTEST Reagent Tablets.

Bottles of 50 tablets with test papers.

HEMATEST Reagent Tablets.

Bottles of 50 tablets with test papers.

ICTOTEST Reagent Tablets.

Bottles of 50 tablets with test mats.

PHENISTIX Reagent Strips.

Bottles of 50 strips with colour scale.

Complete diagnostic kit in sturdy clear plastic container. Contains 1 CLINITEST set, 1 bottle each of CLINISTIX, ALBUSTIX, ACETEST, OCCULTEST and ICTOTEST, together with six test tubes and three droppers.

Test tube rack of sturdy plastic—designed for surgery use with CLINITEST. Complete with six test tubes and two droppers.

DEXTROTEST blood sugar kit.

Sufficient for 30 tests. Includes two graduated test tubes, metal test tube stand, dropper, 30 filter paper discs, 30 Reagent Tablets P and 30 Reagent Tablets S, each wrapped in moisture-proof tinfoil, together with instructions and colour scale.

Refills: Sufficient for 30 tests with above kit.